Antibiotics in Addition to Systemic Corticosteroids for Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Johannes M. A. Daniels[1], Dominic Snijders[1], Casper S. de Graaff[1], Fer Vlaspolder[2], Henk M. Jansen[3], and Wim G. Boersma[1]

[1]Department of Pulmonary Diseases and [2]Department of Microbiology, Medical Center Alkmaar, Alkmaar; and [3]Department of Pulmonary Diseases, Amsterdam Medical Center, University of Amsterdam, Amsterdam, The Netherlands

***Rationale*: The role of antibiotics in acute exacerbations is controversial and their efficacy when added to systemic corticosteroids is unknown.**

***Objectives*: We conducted a randomized, placebo-controlled trial to determine the effects of doxycycline in addition to corticosteroids on clinical outcome, microbiological outcome, lung function, and systemic inflammation in patients hospitalized with an acute exacerbation of chronic obstructive pulmonary disease.**

***Methods*: Of 223 patients, we enrolled 265 exacerbations defined on the basis of increased dyspnea and increased sputum volume with or without increased sputum purulence. Patients received 200 mg of oral doxycycline or matching placebo for 7 days in addition to systemic corticosteroids. Clinical and microbiological response, time to treatment failure, lung function, symptom scores, and serum C-reactive protein were assessed.**

***Measurements and Main Results*: On Day 30, clinical success was similar in intention-to-treat patients (odds ratio, 1.3; 95% confidence interval, 0.8 to 2.0) and per-protocol patients. Doxycycline showed superiority over placebo in terms of clinical success on Day 10 in intention-to-treat patients (odds ratio, 1.9; 95% confidence interval, 1.1 to 3.2), but not in per-protocol patients. Doxycycline was also superior in terms of clinical cure on Day 10, microbiological outcome, use of open label antibiotics, and symptoms. There was no interaction between the treatment effect and any of the subgroup variables (lung function, type of exacerbation, serum C-reactive protein, and bacterial presence).**

***Conclusions*: Although equivalent to placebo in terms of clinical success on Day 30, doxycycline showed superiority in terms of clinical success and clinical cure on Day 10, microbiological success, the use of open label antibiotics, and symptoms.**

Clinical trial registered with www.clinicaltrials.gov (NCT00170222).

Keywords: pulmonary disease; chronic obstructive pulmonary disease; antibacterial agents; infection

Chronic obstructive pulmonary disease (COPD) constitutes a major health problem (1). Acute exacerbations of COPD (AECOPD) have considerable impact on morbidity, mortality, and quality of life (2, 3). Common triggers for AECOPD include air pollution and viral and/or bacterial infection of the airways, but the cause of approximately one third of severe exacerbations cannot be identified (4). The role of bacteria in AECOPD is controversial. In about 50% of exacerbations significant amounts of potential bacterial pathogens can be isolated from protected brush specimens obtained by bronchoscopy (5–7). However, the same pathogens are found in the airways of patients in a stable phase of the disease (5, 8–11). It is impossible for clinicians to distinguish infection from colonization. Nonetheless, antibiotics are widely used to treat patients with AECOPD. Several meta-analyses have confirmed the value of antimicrobial therapy (12–14). Antibiotics seem to be most effective in patients with increased dyspnea, increased sputum volume, and increased sputum purulence (15). Unfortunately, the placebo-controlled trials that investigated the efficacy of antibiotics have important limitations (16–18). Furthermore, these trials were conducted several decades ago, before systemic steroids were widely introduced for the treatment of AECOPD (19–22).

It is unclear whether antibiotics have additional benefits when applied in patients with more severe exacerbations that are already treated with systemic corticosteroids. Sachs and colleagues (23) suggested that antibiotics were redundant when corticosteroids were given, irrespective of sputum color or bacterial involvement. However, their sample size was small (n = 71) and it consisted of both patients with COPD and patients with asthma. In our opinion, therefore, new placebo-controlled trials are justified.

We designed a randomized, double-blind, placebo-controlled trial of doxycycline in addition to systemic corticosteroids for patients hospitalized with an acute exacerbation of COPD. Our goal was to assess the effects of doxycycline on clinical and microbiological response, symptoms, lung function, and systemic inflammation (C-reactive protein). The design of this trial is unique in that it has incorporated several features that were missing in other placebo-controlled trials: first, concomitant treatment, including systemic corticosteroids, was fully standardized. Second, radiographic signs of pneumonia and fever were exclusion

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Although evidence suggests that antibiotics are effective in acute exacerbations of chronic obstructive pulmonary disease, most trials were flawed and performed before systemic corticosteroids were recognized as a beneficial treatment.

What This Study Adds to the Field

This study provides evidence that antibiotics in addition to systemic corticosteroids have a limited and short-lived effect on clinical outcome and symptoms and no effect on lung function and systemic inflammation.

(*Received in original form June 4, 2009; accepted in final form October 29, 2009*)

Supported by an unrestricted grant from GlaxoSmithKline (The Netherlands). The funding source had no part in the study design, conduct, or reporting of the study.

Correspondence and requests for reprints should be addressed to Johannes M. A. Daniels, M.D., Department of Pulmonary Diseases, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. E-mail: j.daniels@vumc.nl

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 181. pp 150–157, 2010
Originally Published in Press as DOI: 10.1164/rccm.200906-0837OC on October 29, 2009
Internet address: www.atsjournals.org

criteria to prevent enrollment of patients with pneumonia. Finally, sputum samples were collected before and after the intervention to allow a thorough microbiological workup. Some of the results of these studies have been previously reported in the form of an abstract (24).

METHODS

Setting and Participants

Participants were enrolled at the Medical Centre Alkmaar in Alkmaar, the Netherlands and the Waterland Hospital in Purmerend, the Netherlands. The study population consisted of patients 45 years of age or older, diagnosed with COPD stages I–IV as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (25), with an acute (onset ≤ 14 d) exacerbation (as defined by Anthonisen and colleagues [15]: type 1 [increased dyspnea, sputum volume, and sputum purulence] or type 2 [two of three symptoms]) that required hospitalization. Criteria for hospital admission are described in the online supplement. The most important exclusion criteria included fever (≥38.5°C) to prevent enrollment of patients with pneumonia, antibiotic treatment for at least 24 hours, and radiographic signs of pneumonia (not specified). All exclusion criteria are listed in the online supplement.

Randomization and Intervention

Within 24 hours of admission, patients were randomly assigned to receive a 7-day course of doxycycline or placebo. Details about the randomization process and allocation concealment are presented in the online supplement. Concomitant treatment consisted of intravenously administered prednisolone (starting with 60 mg/d, tapering by 10 mg per 2 d to 40 mg/d followed by 30 mg of oral prednisolone on Day 7, tapering by 5 mg per 2 d to 0 mg or the maintenance dose before admission), nebulized bronchodilator therapy four to six times daily, and physiotherapy. Other COPD medication was continued, except for short-acting bronchodilators. Because all patients received 6 days of intravenous steroids the minimum length of stay was 7 days.

Throughout the trial, attending physicians were unable to access the results of sputum cultures. However, when a pathogen was isolated that is usually resistant to doxycycline, the attending physician was informed. In case of clinical treatment failure the attending physician was allowed to access the culture results and to replace the study drug by an open label antibiotic. Rerandomization was allowed if a new exacerbation occurred at least 3 months after the first enrollment. Safety was monitored daily with the help of adverse event reports.

Outcomes and Follow-Up

On Days 1, 10, and 30, patients were assessed clinically: blood samples were drawn for measurement of C-reactive protein (CRP, Beckman Coulter Inc., Fullerton, CA) and serologic testing, spirometry was performed and expectorated sputum samples were collected. Symptom scores consisted of visual analog scales (VAS) for dyspnea, cough, fatigue, and sputum purulence. For each symptom the minimal score was 1 and the maximal score was 10. Separate and total scores were calculated. Microbiological procedures are described in detail in the online supplement.

The primary end point was clinical response on Day 30 as defined by Chow and colleagues (26) Treatment success was defined as cure (a complete resolution of signs and symptoms associated with the exacerbation) or improvement (a resolution or reduction of the symptoms and signs without new symptoms or signs associated with the infection). Treatment failure was defined as absence of resolution of symptoms and signs, worsening of symptoms and signs, occurrence of new symptoms and signs associated with the primary or a new infection or death.

Secondary end points included clinical success on Day 10, clinical cure on Days 10 and 30, antibiotic treatment for lack of efficacy, lung function (ΔFEV_1), time to treatment failure (defined previously), serum C-reactive protein (CRP), symptoms, and microbiological response. Criteria for microbiological response are described in the online supplement.

Statistical Analysis

Our sample size calculation was based on the results of Anthonisen and colleagues (15), who found a clinical success rate of 52% for the placebo group and 67% for the antibiotic group (type 1 and type 2 AECOPD combined). We calculated that 167 exacerbations were needed in both arms to detect the previously mentioned difference between antibiotic and placebo treatment on Day 30 with a power of 80% and a two-sided α level of 0.05. During the trial we discovered that the percentage of type 1 exacerbations in our trial was higher than expected. Therefore we expected a higher treatment effect (16.7%). Recalculation of the sample size showed that 132 exacerbations were needed in each arm.

SPSS 16.0 for Windows (SPSS Inc, Chicago, IL) and Stata version 11.0 (StataCorp, College Station, TX) were used for data management and statistical analysis. Differences between the treatment groups were analyzed by logistic regression analysis, correcting for within-patient clustering with generalized estimating equations. Differences in time to treatment failure were compared by Cox proportional hazards regression, adjusting for within-patient clustering by robust standard error estimation. Subgroups were specified according to type of exacerbation, bacterial presence, serum CRP, and lung function. Heterogeneity of treatment effect between subgroups was examined by logistic regression analysis. A significance level of 0.05 was specified for all comparisons. We did not correct for multiple comparisons because several sets of end points are closely related and do not represent separate hypotheses.

One planned interim analysis, regarding the primary end point and mortality, that was performed by an independent statistician after enrollment of 140 exacerbations showed no significant differences and the study was therefore continued as planned.

RESULTS

Baseline Characteristics

Of the 367 exacerbations that were screened, 265 exacerbations of 223 patients were enrolled and randomly assigned to placebo (137 exacerbations) or doxycycline (128 exacerbations). After two enrollments, inclusion at the Waterland Ziekenhuis in Purmerend was terminated for logistical reasons. The majority of the patients in the placebo group (110 of 137 [80%]) and the doxycycline group (111 of 128 [87%]) completed the trial (Figure 1). The most common reason for withdrawal was lack of efficacy, which was more common in the placebo group (23 of 137 [17%]) than in the doxycycline group (8 of 128 [6%]). The baseline characteristics are shown in Table 1. Of the 265 enrolled exacerbations, 178 (67%) were type 1 and 87 (33%) were type 2.

Primary Outcome

On Day 30, clinical success was observed in 78 patients (61%) from the doxycycline group and 72 patients (53%) from the placebo group (odds ratio [OR], 1.3; 95% confidence interval [95% CI], 0.8 to 2.0; $P = 0.32$) (Table 2). In the per-protocol population we found similar results (OR, 1.2; 95% CI, 0.7 to 1.9; $P = 0.47$).

Secondary Outcome

Clinical outcome on Day 10. On Day 10, clinical success was observed in 103 patients (80%) from the doxycycline group and 94 patients (69%) from the placebo group (OR, 1.9; 95% CI, 1.1 to 3.2; $P = 0.03$). This significant difference was lost in the per-protocol population (OR, 1.8; 95% CI, 1.0 to 3.1; $P = 0.05$).

Clinical cure. Clinical cure was observed in 86 patients (67%) from the doxycycline group and 69 patients (51%) from the placebo group on Day 10 (OR, 1.9; 95% CI, 1.2 to 3.2; $P = 0.01$). On Day 30 clinical cure was observed in 65 patients (51%) from the doxycycline group and 56 patients (41%) from the placebo group (OR, 1.4; 95% CI, 0.9 to 2.3; $P = 0.15$).

Time to treatment failure. Time to treatment failure (defined as absence of resolution of symptoms and signs, worsening of symptoms and signs, occurrence of new symptoms and signs associated with the primary or a new infection or death) was not

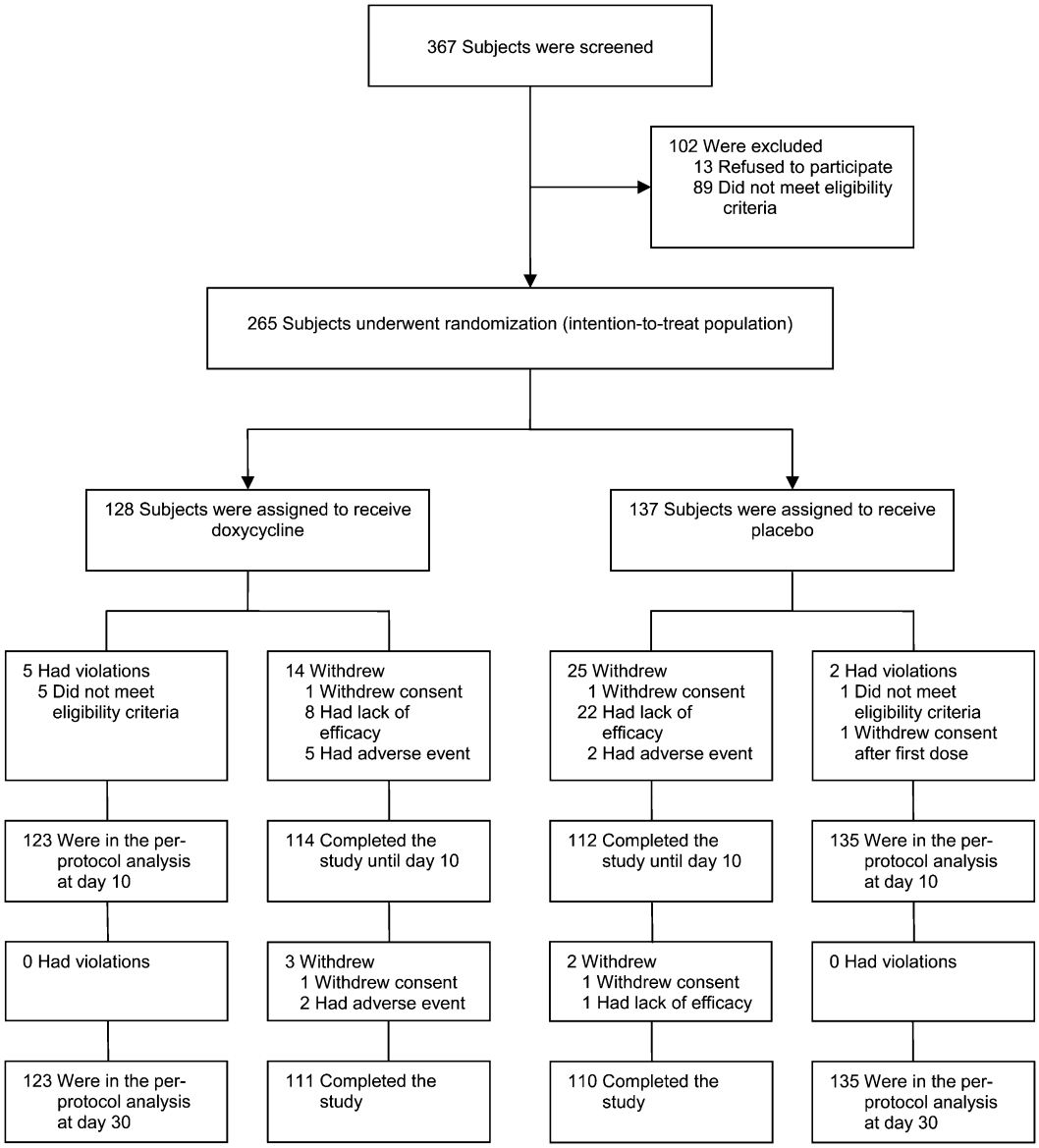

Figure 1. Enrollment and follow-up of patients. Shows the screening, enrollment, random assignment, and follow-up of patients.

significantly longer in the doxycycline group than in the placebo group ($P = 0.19$ by the log-rank test) (Figure 2). Forty-six patients (37%) in the doxycycline group and 62 patients (46%) in the placebo group had treatment failure.

Antibiotic treatment for lack of efficacy. Open label antibiotic treatment for lack of efficacy was applied in 19 patients (15%) of the doxycycline group and 38 patients (28%) in the placebo group by Day 10 (OR, 0.5; 95% CI, 0.3 to 0.9; $P = 0.01$) and 42 patients (33%) in the doxycycline group and 61 patients (45%) of the placebo group by Day 30 (OR, 0.7; 95% CI, 0.4 to 1.1; $P = 0.13$) (Table 2).

Lung function. Paired lung function data were available for 224 patients (85%) on Days 1 and 10 and in 189 patients (71%) on Days 1 and 30. The mean increase in FEV_1 on Day 10 was 0.16 ± 0.26 L in the doxycycline group and 0.11 ± 0.26 L in the placebo group (mean difference, 0.05 L; 95% CI, –0.02 to 0.12; $P = 0.16$) (Table 2). On Day 30, the mean increase was 0.15 ± 0.33 L in the doxycycline group and 0.08 ± 0.25 L in the placebo group (mean difference, 0.07 L; 95% CI, −0.03 to 0.13; $P = 0.22$) (Table 2).

Serum C-reactive protein. The mean change in serum CRP on Day 10 was -56.4 ± 65.5 mg/L in the doxycycline group and -38.9 ± 72.7 mg/L in the placebo group ($P = 0.07$) (Table 2). This trend was no longer present on Day 30.

Symptom scores. The mean change in total symptoms score on Day 10 was -10.1 ± 9.0 in the doxycycline group and -6.2 ± 8.6 in the placebo group (mean difference, −2.3; 95% CI, −3.9 to −0.8; $P = 0.003$) (Table 2). On Day 30, the mean change was -9.4 ± 9.7 in the doxycycline group and -8.3 ± 8.6 in the placebo group (mean difference, −1.0; 95% CI, −3.7 to 1.8; $P = 0.50$). Separate mean symptom scores of cough and sputum purulence were significantly more reduced in those treated with doxycycline on Day 10, but not on Day 30 (Table 2).

Microbiological outcome. Two hundred and fourteen potential bacterial pathogens were isolated in 158 exacerbations. The most predominant bacteria were *Haemophilus influenzae* (41%), *Streptococcus pneumoniae* (24%) and *Moraxella catarrhalis* (22%). A viral infection was serologically diagnosed in 20 patients (influenza A virus, n = 6; parainfluenza virus, n = 5; respiratory syncytial virus, n = 5; adenovirus, n = 3; influenza B virus, n = 1). Resistance to tetracycline was observed in 1% of *H. influenzae* isolates, 7% of *S. pneumoniae* isolates, 7% of *M. catarrhalis* isolates, 0% of *Staphylococcus aureus* isolates, and 48% of *Pseudomonas* spp. isolates. We were able to evaluate

TABLE 1. BASELINE PATIENT CHARACTERISTICS

Characteristic	Doxycycline Group (*n = 107*)	Placebo Group (*n = 116*)
Age, years	71.0 ± 10.2	72.8 ± 9.2
Male sex, no. (%)	61 (57)	72 (62)
Smokers, no. (%)	96 (90)	105 (91)
Current smokers, no. (%)	31 (30)	39 (35)
Pack-years, median (IQR)	39 (25–50)	40 (28–50)
Body mass index*	25.0 ± 5.7	24.7 ± 6.8
Percent predicted FEV_1, %†	43.9 ± 17.2	46.9 ± 18.5
Percent predicted FVC, %†	71.1 ± 17.7	72.7 ± 18.6
Comorbidities, no. (%)		
Ischemic heart disease	22 (20)	20 (18)
Heart failure	9 (8)	6 (5)
Cerebrovascular disease	1 (1)	3 (3)
Diabetes mellitus	11 (10)	5 (4)
C-reactive protein (mg/L), median (IQR)	30 (9–84.5)	23.5 (6.3–78.5)
Pa_{O_2} (mm Hg), median (IQR)	68 (61–76)	67 (59–75)
Pa_{CO_2} (mm Hg), median (IQR)	41 (37–47)	40 (36–45)
Breathing frequency, median (IQR)	24 (22–28)	24 (18–28)
ICS, no. (%)	83 (80)	92 (86)
SCS, for maintenance use, no. (%)	14 (13)	7 (6)
SCS, course for current AECOPD, no. (%)	20 (19)	24 (21)

Definition of abbreviations: AECOPD = acute exacerbation of COPD; FEV_1 = postbronchodilator forced expiratory volume in 1 second; ICS = inhalation corticosteroids; IQR = interquartile range; SCS = systemic corticosteroids.

Plus–minus values represent means ± SD.

* The body mass index is the weight in kilograms divided by the square of the height in meters.

† Last recorded postbronchodilator value in a stable state before admission.

the bacteriological response in 151 patients (Table 3). In the doxycycline group bacteriological success was accomplished in 52 of 78 patients (67%) and in the placebo group in 25 of 73 patients (34%) (OR, 3.8; 95% CI, 1.9 to 7.5; $P < 0.001$) (Table 3). For the three most predominant pathogens (*H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*) the success rates were significantly better in the doxycycline group (Table 3). In the doxycycline group bacterial persistence rates were 31% for *H. influenzae*, 17% for *S. pneumoniae*, *and* 9% for *M. catarrhalis*.

Subgroup Analysis

On Day 10 doxycycline showed superiority in patients with type 1 AECOPD and patients with a CRP value of 50 mg/L or more (Figure 3a). However, the treatment effect did not differ among these subgroups. On Day 30 doxycycline was still superior to placebo in patients with a CRP of at least 50 mg/L, but not in patients with type 1 AECOPD (Figure 3B). Again, no interaction between the treatment effect and any of the subgroup variables was found.

Safety

Adverse reactions that were considered to be related to the study medication occurred in four patients (3%) in the doxycycline group and five patients (4%) in the placebo group. Adverse reactions in both groups were heartburn, diarrhea, and nausea. All reactions were mild and self-limiting. In only one patient was the study medication discontinued, because of an adverse reaction (placebo group, complaints of heartburn).

Serious adverse events occurred in 11 patients (9%) from the doxycycline group (11 events, including 7 deaths) and 7 patients (5%) from the placebo group (7 events, including 3 deaths). Serious adverse events in the doxycycline group included pneumonia, urinary tract infection, myocardial infarction, and hypoglycemia. One patient died of gram-negative sepsis, four patients died of respiratory failure, and two patients died of acute heart failure. Serious adverse events in the placebo group included pneumonia and stomach perforation. One patient died of pneumonia and two died of respiratory failure.

DISCUSSION

We found no significant difference in clinical outcome on Day 30 among patients with AECOPD who were randomly assigned to doxycycline as compared with those who were assigned to placebo. Doxycycline was superior to placebo in terms of clinical success and clinical cure on Day 10 as well as microbiological success. In addition, open label antibiotic therapy for lack of efficacy occurred significantly less often in patients assigned to doxycycline. Finally, patients taking doxycycline had a greater reduction in symptoms on Day 10. We did not see a difference in recovery of lung function, resolution of systemic inflammation, and time to treatment failure between the treatment groups.

This is the first placebo-controlled trial of antibiotics in addition to systemic corticosteroids for acute exacerbations of COPD. We did not find a significant treatment effect at the primary end point (clinical success on Day 30). This observation could be explained by several factors: first, systemic steroids have proven to be highly beneficial in hospitalized patients (19–22). The benefit of antibiotics on top of systemic steroids might be smaller than that observed in other studies where systemic steroids were often withheld or applied only in a minority of patients. Second, we excluded patients with fever and patients with chest radiographs suggestive of pneumonia. This was not done in other placebo-controlled trials. Consequential enrollment of patients with pneumonia might have inflated the observed treatment effects. Third, we studied patients with moderate to severe COPD with exacerbations that required hospitalization. The severe nature of these exacerbations might have caused a large proportion to relapse early, thereby attenuating the treatment effect. A fourth explanation could be insufficient antibacterial activity of doxycycline. Tetracyclines were used in the majority of placebo-controlled trials so far and the resistance rates of the commonly isolated bacterial pathogens in our region are low. Nonetheless, although persistence rates for *S. pneumoniae* and *M. catarrhalis* were low, we did prove persistence in 31% of patients with *H. influenzae* who received doxycycline whereas the *in vitro* resistance rate of *H. influenzae* was only 1%.

TABLE 2. EFFECTS OF INTERVENTION ON PRIMARY AND SECONDARY END POINTS IN THE INTENTION-TO-TREAT POPULATION

End Point	Doxycycline (*n = 128*)	Placebo (*n = 137*)	Odds Ratio or Mean Difference (95% CI)*	*P* Value*
Primary				
Clinical success on Day 30, no. (%)	78 (61)	72 (53)	1.3 (0.8 to 2.0)	0.32
Secondary				
Clinical success on Day 10, no. (%)	103 (80)	94 (69)	1.9 (1.1 to 3.2)	0.03
Clinical cure on Day 10, no. (%)	86 (67)	69 (51)	1.9 (1.2 to 3.2)	0.01
Clinical cure on Day 30, no. (%)	65 (51)	56 (41)	1.4 (0.9 to 2.3)	0.15
Open-label antibiotic treatment for lack of efficacy, no. (%)				
On Day 10	19 (15)	38 (28)	0.5 (0.3 to 0.9)	0.01
On Day 30	42 (33)	61 (45)	0.7 (0.4 to 1.1)	0.13
FEV_1, L				
At inclusion	0.95 (0.45)	1.01 (0.44)		
Change on Day 10	0.16 (0.26)	0.11 (0.26)	0.05 (−0.02 to 0.12)	0.16
Change on Day 30	0.15 (0.33)	0.08 (0.25)	0.07 (−0.03 to 0.13)	0.22
Serum CRP, mg/L				
At inclusion	62.2 (68.1)	62.9 (76.7)		
Change on Day 10	−56.4 (65.5)	−38.9 (72.7)	−15.9 (−32.9 to 1.1)	0.07
Change on Day 30	−28.6 (83.3)	−37.0 (87.1)	10.3 (−12.8 to 33.4)	0.38
Symptom scores†				
Total score				
At inclusion	25.4 (7.3)	24.2 (7.5)		
Change on Day 10	−10.1 (9.0)	−6.2 (8.6)	−2.3 (−3.9 to −0.8)	0.003
Change on Day 30	−9.4 (9.7)	−8.3 (8.6)	−1.0 (−3.7 to 1.8)	0.50
Dyspnea				
At inclusion	7.2 (2.3)	6.8 (2.3)		
Change on Day 10	−2.8 (3.0)	−2.0 (2.7)	−0.3 (−0.9 to 0.3)	0.32
Change on Day 30	−2.4 (2.8)	−1.8 (2.8)	−0.5 (−1.3 to 0.3)	0.24
Fatigue				
At inclusion	6.8 (2.6)	6.4 (2.6)		
Change on Day 10	−2.3 (3.1)	−1.6 (2.9)	−0.7 (−1.6 to 0.1)	0.12
Change on Day 30	−1.6 (3.5)	−1.2 (3.2)	−0.3 (−1.3 to 0.7)	0.62
Cough				
At inclusion	6.5 (2.4)	6.2 (2.5)		
Change on Day 10	−3.0 (2.9)	−1.9 (2.9)	−1.1 (−1.8 to −0.3)	0.02
Change on Day 30	−3.4 (3.0)	−3.0 (3.1)	−0.4 (−1.3 to 0.6)	0.46
Sputum purulence				
At inclusion	5.1 (2.8)	5.0 (3.0)		
Change on Day 10	−2.4 (3.2)	−0.9 (3.2)	−1.3 (−2.1 to −0.5)	0.003
Change on Day 30	−2.5 (3.2)	−2.3 (3.5)	−0.1 (−1.2 to 0.9)	0.80

Definition of abbreviations: 95% CI = 95% confidence interval; CRP = C-reactive protein.
Values are listed as mean ± SD unless stated otherwise.
* Corrected for within-patient clustering.
† Symptoms scores were assessed with a visual analog scale (scale 1–10).

Persistence of *H. influenzae* strains after antibiotic therapy, even if the strain is susceptible to the prescribed antibiotic, is a well-known phenomenon (27, 28). An *in vitro* study showed that penetration of *H. influenzae* between epithelial cells protects the bacteria from antibody-mediated defense mechanisms and antibiotics (29). There is sufficient evidence to suggest that fluoroquinolones such as moxifloxacin outperform conventional antibiotics in terms of bacterial eradication, especially of *H. influenzae*. In spite of this there is no evidence of clinical superiority over conventional antibiotics and only limited evidence of superiority in long-term outcomes such as time to the next exacerbation (30). In light of this evidence, it seems unjustified to advocate the use of quinolones for AECOPD in regions with acceptable resistance rates to conventional antibiotics.

As doxycycline was not superior to placebo in the overall analysis, it is important to assess whether certain subgroups benefit from antibiotics. An important finding of Anthonisen and colleagues (15) was that antibiotics are most effective in patients with increased sputum purulence (type 1 AECOPD). In the current study, we found that doxycycline was superior on Day 10 in patients with a type 1 exacerbation and equivalent in patients with a type 2 exacerbation. The treatment effect, however, did not differ significantly between these groups (P = 0.14). We therefore cannot claim interaction between the treatment effect of doxycycline and the type of exacerbation. Because sputum purulence is a marker for bacterial infection,

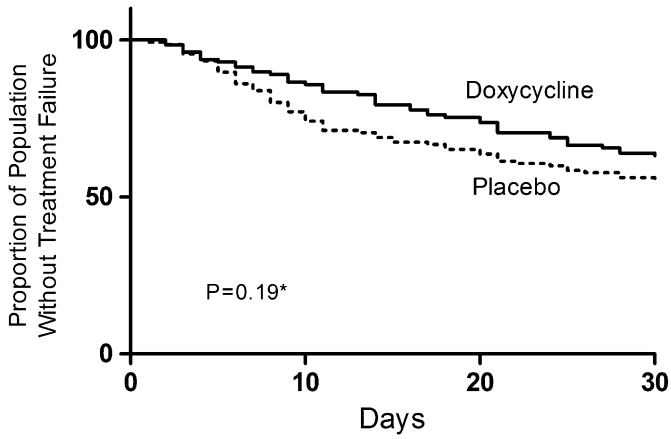

Figure 2. Kaplan-Meier curves showing the effect of the intervention on time to treatment failure in the intention-to-treat population. *Corrected for within-patient clustering.

TABLE 3. BACTERIOLOGICAL RESPONSE ON DAY 10 IN SUBJECTS FROM THE INTENTION-TO-TREAT POPULATION WITH BACTERIAL INFECTION

End Point	n	Doxycycline (*n* = 78) n/total (%)	Placebo (*n* = 73) n/total (%)	Odds Ratio (95% CI)*	*P* Value*
Overall success, no. (%)	151	52/78 (67)	25/73 (34)	3.8 (1.9 to 7.5)	<0.001
Success per pathogen					
Haemophilus influenzae	86	28/44 (64)	14/42 (33)	3.5 (1.4 to 8.5)	0.006
Streptococcus pneumoniae	50	18/23 (78)	9/27 (33)	6.9 (1.9 to 24.8)	0.003
Moraxella catarrhalis	46	18/22 (82)	10/24 (42)	5.1 (1.4 to 18.9)	0.015
Pseudomonas spp.	7	1/4 (25)	2/3 (67)		
Staphylococcus aureus	6	4/4 (100)	2/2 (100)		
Haemophilus parainfluenzae	6	5/5 (100)	1/1 (100)		
Serratia marcescens	2		2/2 (100)		
Escherichia coli	2	1/1 (100)	1/1 (100)		
Enterobacterium spp.	1		1/1 (100)		
Xanthomonas maltophilia	1	1/1 (100)			
Mycoplasma pneumoniae†	3	0/1 (0)	1/2 (50)		
Chlamydia pneumoniae†	2		1/2 (50)		

A potential pathogen was identified in 158 exacerbations. The bacteriological response could be evaluated in 151 exacerbations.

* Corrected for within-patient clustering.

† Serologic tests were used for the diagnosis of *M. pneumoniae* and *C. pneumoniae* infection.

we also established subgroups according to the presence of a bacterial pathogen in expectorated sputum. Again, we found no interaction with the treatment effect. This finding suggests that the presence of bacteria in the sputum of patients with AECOPD does not necessarily represent a new infection that warrants treatment with antibiotics. It is evident that the airways of patients with COPD are often colonized with bacteria and that increase in bacterial load or even acquisition of a

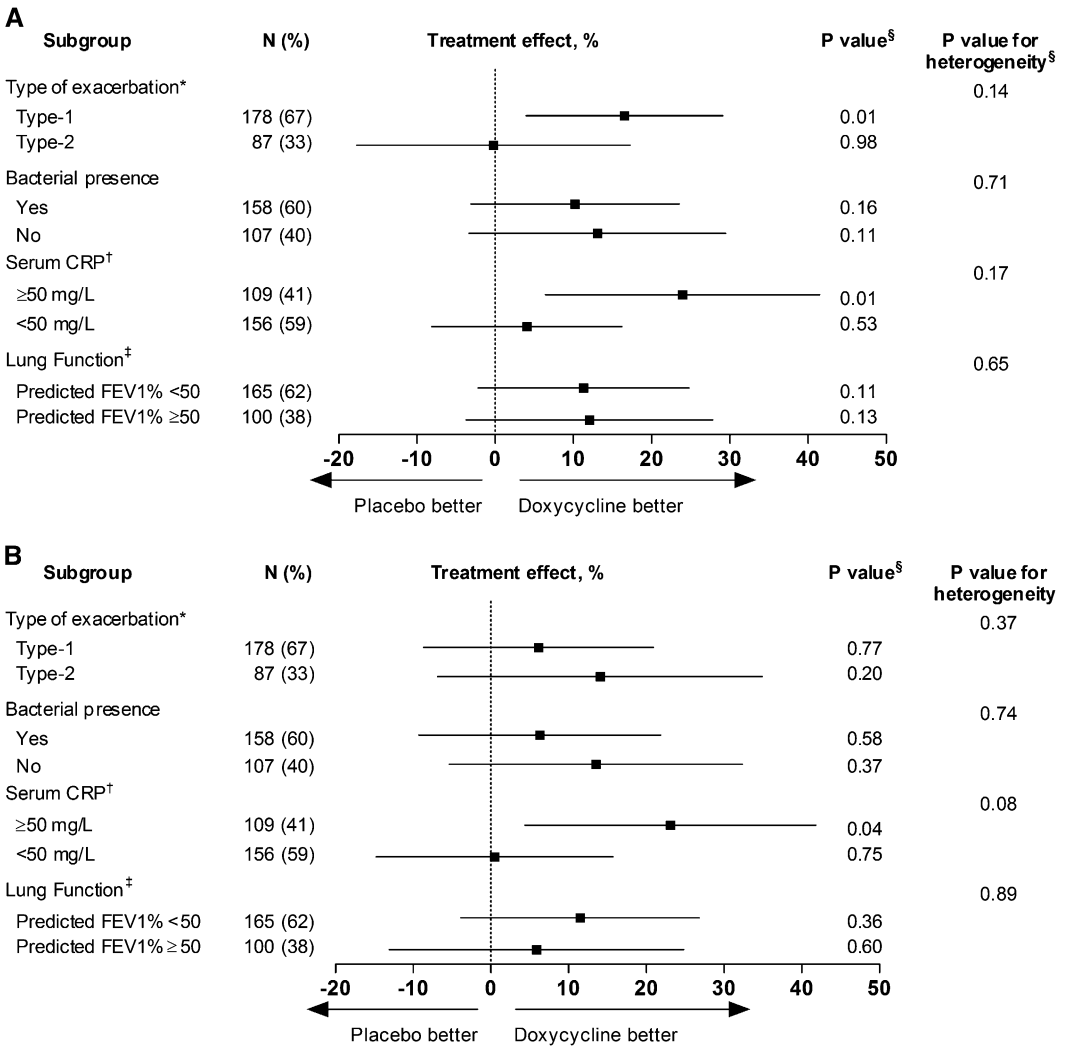

Figure 3. Subgroup analysis on (*A*) Day 10 and (*B*) Day 30. Shown are treatment effect (*solid squares*), 95% confidence intervals (*horizontal lines*), *P* values, and *P* values for interaction between the treatment effect and the subgroup variable. *Type of exacerbation was defined according to Anthonisen and colleagues (15); †the cutoff value was prespecified at 10 mg/L. Increasing the cutoff value clearly altered the results, with the best results at 50 mg/L; ‡predicted FEV_1% = postbronchodilator forced expiratory volume in 1 second, % of predicted (last recorded value in a stable state before admission). The cutoff value of predicted FEV_1% was prespecified at 50%. Lowering the cutoff value did not alter the results. AECOPD = acute exacerbation of COPD; §corrected for within-patient clustering.

new strain does not necessarily lead to an exacerbation (5, 8–11, 31–33). We also constructed subgroups according to serum CRP levels. We hypothesized that infection with a new strain, as opposed to colonization, results in more pronounced systemic inflammation, which was confirmed by others (34). Whereas we observed that doxycycline was superior on Day 10 in patients with a CRP value equal to or exceeding 50 mg/L, it was equivalent in patients with a CRP value less than 50 mg/L. Although we were unable to prove interaction between serum CRP levels and treatment effect, this might suggest that only patients with marked systemic inflammation harbor a bacterial infection that requires antimicrobial therapy. These findings bear resemblance with evidence that antibiotic treatment guided by levels of procalcitonin, a systemic marker of bacterial infection, safely reduces antibiotic use (35, 36). Although CRP has been proposed as a marker of infection in AECOPD (37, 38), this is the first randomized controlled trial that indicates its possible value in selecting patients for antibiotic therapy. CRP-guided therapy would reduce the use of antibiotics because in our population CRP was at least 50 mg/L in only 41% of exacerbations, whereas 67% of exacerbations were type 1. Because we observed only a trend, possibly because the current trial was not powered to investigate a difference of treatment effect between subgroups according to CRP value, additional studies are needed to further investigate the role of CRP in the management of AECOPD.

The finding of the present study must be interpreted in the context of several potential limitations. The two-center design and the absence of advanced antimicrobial resistance in our region might affect the generalizability to other populations. Advantages of the two-center design include efficiency and standardization of laboratory methods. Another limitation is that patients were not stratified according to factors that are known to influence outcome such as disease severity. In the subgroup analysis, however, we found that the treatment effect was not affected by disease severity. Finally, the symptom scores assessed by VAS as used in the present study are not validated instruments for evaluating symptoms in patients with AECOPD. Nonetheless, the VAS is used frequently for measuring subjective symptoms and there is evidence that the VAS can reproducibly measure symptoms such as dyspnea and fatigue during steady state exercise (39).

In conclusion, doxycycline is equivalent to placebo in terms of clinical response on Day 30, but superior in terms of clinical success and clinical cure on Day 10 as well as microbiological success on Day 10. Additional effects of doxycycline include reduction of open label antibiotic therapy for lack of efficacy and a greater reduction in symptoms. Subgroup analysis revealed no interaction between the subgroup variables and the treatment effect, although there was a trend for patients with a high CRP value to benefit from antibiotic therapy.

***Conflict of Interest Statement*:** None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

***Acknowledgment*:** The authors thank the patients who enrolled in this study, and the physicians, nurses, and secretaries of the Department of Pulmonary Diseases for important contributions. The authors thank T. van der Ploeg and D. L. Knol for work on the statistical analysis and T. Tossijn-Groot and P. Singer of the Department of Microbiology for their hard work.

References

1. Murray CJ, Lopez AD. Evidence-based health policy: lessons from the Global Burden of Disease Study. *Science* 1996;274:740–743.
2. Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;161: 1608–1613.
3. Fletcher CM, Peto R, Tinker CM, Speizer FE. Natural history of chronic bronchitis and emphysema. Oxford: Oxford University Press; 1976.
4. White AJ, Gompertz S, Stockley RA. Chronic obstructive pulmonary disease. 6. The aetiology of exacerbations of chronic obstructive pulmonary disease. *Thorax* 2003;58:73–80.
5. Monso E, Ruiz J, Rosell A, Manterola J, Fiz J, Morera J, Ausina V. Bacterial infection in chronic obstructive pulmonary disease: a study of stable and exacerbated outpatients using the protected specimen brush. *Am J Respir Crit Care Med* 1995;152:1316–1320.
6. Pela R, Marchesani F, Agostinelli C, Staccioli D, Cecarini L, Bassotti C, Sanguinetti CM. Airways microbial flora in COPD patients in stable clinical conditions and during exacerbations: a bronchoscopic investigation. *Monaldi Arch Chest Dis* 1998;53:262–267.
7. Soler N, Torres A, Ewig S, Gonzalez J, Celis R, El-Ebiary M, Hernandez C, Rodriguez-Roisin R. Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. *Am J Respir Crit Care Med* 1998; 157:1498–1505.
8. Riise GC, Larsson S, Larsson P, Jeansson S, Andersson BA. The intrabronchial microbial flora in chronic bronchitis patients: a target for *N*-acetylcysteine therapy? *Eur Respir J* 1994;7:94–101.
9. Cabello H, Torres A, Celis R, El-Ebiary M, Puig de la Bellacasa J, Xaubet A, González J, Agustí C, Soler N. Bacterial colonization of distal airways in healthy subjects and chronic lung disease: a bronchoscopic study. *Eur Respir J* 1997;10:1137–1144.
10. McHardy VU, Inglis JM, Calder MA, Crofton JW, Gregg I, Ryland DA, Taylor P, Chadwick M, Coombs D, Riddell RW. A study of infective and other factors in exacerbations of chronic bronchitis. *Br J Dis Chest* 1980;74:228–238.
11. Gump DW, Phillips CA, Forsyth BR, McIntosh K, Lamborn KR, Stouch WH. Role of infection in chronic bronchitis. *Am Rev Respir Dis* 1976; 113:465–474.
12. Ram FS, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;19:CD004403.
13. McCrory DC, Brown C, Gelfand SE, Bach PB. Management of acute exacerbations of COPD: a summary and appraisal of published evidence. *Chest* 2001;119:1190–1209.
14. Saint S, Bent S, Vittinghoff E, Grady D. Antibiotics in chronic obstructive pulmonary disease exacerbations: a meta-analysis. *JAMA* 1995; 273:957–960.
15. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;106:196–204.
16. Hirschmann JV. Do bacteria cause exacerbations of COPD? *Chest* 2000; 118:193–203.
17. Wilson R. Treatment of COPD exacerbations: antibiotics. *Eur Respir Rev* 2005;14:32–38.
18. Hirschmann JV. Bacteria and COPD exacerbations redux. *Chest* 2001; 119:663–666.
19. Quon BS, Gan WQ, Sin DD. Contemporary management of acute exacerbations of COPD: a systematic review and metaanalysis. *Chest* 2008;133:756–766.
20. Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, Light RW, Anderson P, Morgan NA. Department of Veterans Affairs Cooperative Study Group. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1999;340:1941–1947.
21. Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Lancet* 1999;354:456–460.
22. Maltais F, Ostinelli J, Bourbeau J, Tonnel AB, Jacquemet N, Haddon J, Rouleau M, Boukhana M, Martinot JB, Duroux P. Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Am J Respir Crit Care Med* 2002;165:698–703.
23. Sachs AF, Koëter GH, Groenier KH, van der Waaij D, Schiphuis J, Meyboom-de Jong B. Changes in symptoms, peak expiratory flow, and sputum flora during treatment with antibiotics of exacerbations in patients with chronic obstructive pulmonary disease in general practice. *Thorax* 1995;50:758–763.
24. Daniels JM, Snijders D, Vlaspolder F, de Graaff CS, Jansen HM, Boersma WG. Antibiotics versus placebo for the treatment of severe acute exacerbations of COPD [abstract]. *Am J Respir Crit Care Med* 2009;179:A5357.

25. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001;163:1256–1276.
26. Chow AW, Hall CB, Klein JO, Kammer RB, Meyer RD, Remington JS.; budesonide Infectious Diseases Society of America and the Food and Drug Administration. Evaluation of new anti-infective drugs for the treatment of respiratory tract infections. *Clin Infect Dis* 1992;15: S62–S88.
27. Groeneveld K, van Alphen L, Eijk PP, Visschers G, Jansen HM, Zanen HC. Endogenous and exogenous reinfections by *Haemophilus influenzae* in patients with chronic obstructive pulmonary disease: the effect of antibiotic treatment on persistence. *J Infect Dis* 1990;161: 512–517.
28. White AJ, Gompertz S, Bayley DL, Hill SL, O'Brien C, Unsal I, Stockley RA. Resolution of bronchial inflammation is related to bacterial eradication following treatment of exacerbations of chronic bronchitis. *Thorax* 2003;58:680–685.
29. van Schilfgaarde M, Eijk P, Regelink A, van Ulsen P, Everts V, Dankert J, van Alphen L. *Haemophilus influenzae* localized in epithelial cell layers is shielded from antibiotics and antibody-mediated bactericidal activity. *Microb Pathog* 1999;26:249–262.
30. Siempos II, Dimopoulos G, Korbila IP, Manta K, Falagas ME. Macrolides, quinolones and amoxicillin/clavulanate for chronic bronchitis: a meta-analysis. *Eur Respir J* 2007;29:1127–1137.
31. Sethi S, Evans N, Grant BJB, Murphy TF. New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 2002;347:465–471.
32. Bresser P, van Alphen L, Lutter R. New strains of bacteria and exacerbations of COPD. *N Engl J Med* 2002;347:2077–2079.
33. Sethi S, Sethi R, Eschberger K, Lobbins P, Cai X, Grant BJ, Murphy TF. Airway bacterial concentrations and exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;176: 356–361.
34. Sethi S, Wrona C, Eschberger K, Lobbins P, Cai X, Murphy T. Inflammatory profile of new bacterial strain exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008;177: 491–497.
35. Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Müller C, Huber P, Müller B, Tamm M. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest* 2007;131:9–19.
36. Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, Müller B. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 2004; 363:600–607.
37. Weis N, Almdal T. C-reactive protein—can it be used as a marker of infection in patients with exacerbation of chronic obstructive pulmonary disease? *Eur J Intern Med* 2006;17:88–91.
38. Dev D, Wallace E, Sankaran R, Cunniffe J, Govan JR, Wathen CG, Emmanuel FX. Value of C-reactive protein measurements in exacerbations of chronic obstructive pulmonary disease. *Respir Med* 1998; 92:664–667.
39. Grant S, Aitchison T, Henderson E, Christie J, Zare S, McMurray J, Dargie H. A comparison of the reproducibility and the sensitivity to change of visual analogue scales, Borg scales, and Likert scales in normal subjects during submaximal exercise. *Chest* 1999;116:1208–1217.