Relationship between respiratory muscle function and quality of life in sarcoidosis


ABSTRACT: In sarcoidosis, pulmonary and general symptoms often do not correlate with radiographic stage and routine lung function tests. Asymptomatic muscle involvement in sarcoidosis is common, but little is known about respiratory muscle involvement. The aim of this study was to investigate any relationships between persistent complaints and/or quality of life and respiratory muscle strength and endurance, respectively.

Measurements of maximal inspiratory and expiratory mouth pressures (Pimax and PEmax), respiratory muscle endurance and routine lung function were made in 18 patients with sarcoidosis. To assess health status and quality of life, patients completed the Sickness Impact Profile (SIP).

Respiratory muscle strength and endurance time were lower in the patient group than in a group of healthy controls (p=0.05). Compared to a general population, the patients with sarcoidosis were found to be limited in physical and psychosocial functioning. The respiratory muscle endurance time correlated with the SIP subscales "mobility" (r=-0.56; p<0.01), and "body care and movement" (r=-0.79; p<0.001). The total lung capacity (TLC), inspiratory vital capacity (IVC) and forced expiratory volume in one second (FEV1) were normal in all subjects.

In conclusion, patients with sarcoidosis and normal lung function showed reduced respiratory muscle strength and endurance time. Correlations were found between these indices and both symptoms and certain Sickness Impact Profile domains. Therefore, we suggest inclusion of measurements of respiratory muscle strength in the assessment and follow-up of patients with sarcoidosis.


Sarcoidosis is a multisystem disorder, which can affect essentially every organ of the body [1]. The parts of the body most frequently involved are the lungs, lymph nodes, skin, eyes, muscles, heart and joints, and, therefore, symptoms vary considerably. In sarcoidosis, disease activity does not necessarily indicate a progressive or fatal course [2]. Even though the active disease often subsides spontaneously, an indication of activity is necessary in order to monitor the course of the disease and guide treatment, should the clinical situation justify it [2, 3]. Whilst there is no single test that accurately reflects the progression of sarcoidosis, clinical examination, chest radiography and lung function tests are used to evaluate and monitor the disease process. Techniques useful in assessing the extent and severity of granulomatous inflammation and fibrosis are: 1) serum markers, including serum angiotensin converting enzyme (sACE); 2) 67Ga scan; 3) bronchoalveolar lavage (BAL); and 4) high resolution computed tomography (HRCT) [2, 4]. When indicators of disease activity, such as radiographic abnormalities, lung function impairment and sACE, return to normal, nonspecific symptoms, such as fatigue and reduced exercise tolerance, may persist.

In a previous study, we found that the quality of life measured by the Sickness Impact Profile (SIP) was related to the perception of complaints, but not to disease activity as conventionally assessed [5]. The SIP is a generic health status instrument, which is intended to measure the impact of sickness rather than to objectively measure the presence of disease [6]. It is an individual's own experience of illness perceived through its effect on daily activities, feelings and attitudes [7].

Asymptomatic granulomatous muscle involvement in sarcoidosis has been reported with a prevalence of 50-80% [8], whereas symptomatic muscle involvement is much less common (range 1.4-2.3%) [9]. The symptomatic involvement that has been described varies from a palpable nodular type to an acute myositis, and a chronic myopathic type [9-12]. Usually, patients present with pain, weakness and muscle atrophy [13]. Little is known, however, about the frequency of respiratory muscle involvement [14].

The aim of this study was to investigate whether there is a relationship between persistent complaints or quality of life disturbance and respiratory muscle function in a population of patients with sarcoidosis. Therefore,
the relationships between respiratory muscle strength, endurance time, and the SIP scores and subscores were evaluated.

Materials and methods

Subjects

Eighteen out-patients suffering from sarcoidosis, who attended the Academic Hospital Nijmegen, were studied. The diagnosis of sarcoidosis was based on consistent clinical features, together with biopsy-proven noncaseating epithelioid cell granuloma. The clinical symptoms of the respective patients varied from none (sarcoidosis detected on routine chest radiography) to more or less severe respiratory symptoms or erythema nodosum and arthralgia (i.e. Lofgren’s syndrome). None of the participating subjects had any significant medical history that might have influenced quality of life. Patients with significant co-morbidity were excluded.

A control group (n=18), comprising healthy employees of the Academic Hospital Nijmegen matched for age and gender, were used as reference for the lung function tests, respiratory muscle strength and endurance time, as well as peripheral muscle strength. A control group comprising 594 subjects from a general Dutch population (mean age 43 yrs, range 18–75 yrs; 267 males (45%) and 327 females (55%)) were used as reference to compare the SIP measurements [15].

Study design

Initially, 26 patients with sarcoidosis were contacted. Eight declined for various personal reasons. Eighteen out-patients agreed to participate after giving informed consent. The questionnaires were completed under supervision of a study assistant, to avoid missing data or misunderstanding. In addition, the patients were asked about their smoking history and whether they had any of the following complaints: fatigue, dyspnoea, cough, arthralgia, or erythema nodosum.

At the time the study was performed, seven of the patients still had symptoms, most notably fatigue. Eleven of the 18 patients had not taken corticosteroids during the previous 3 months. The other seven patients were taking corticosteroids during the 3 months prior to the study, with an average prednisone dose of 5.7 mg·day⁻¹. Five of these seven patients still had symptoms. The mean (±SD) SACE level was 16.8±5.9 U·L⁻¹ (reference value <20 U·L⁻¹). The radiographic stage varied from 0 to III: four patients had stage 0, two stage I, 10 stage II, and two stage III appearances. Demographic and clinical characteristics of the patients and the control group are summarized in table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sarcoidosis patients</th>
<th>Control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>43 (11)</td>
<td>41 (11)</td>
</tr>
<tr>
<td>Gender male/female</td>
<td>1/17</td>
<td>8/10</td>
</tr>
<tr>
<td>Smoking yes/no</td>
<td>1/17</td>
<td>9/9</td>
</tr>
<tr>
<td>Complaints yes/no</td>
<td>7/11</td>
<td>-</td>
</tr>
<tr>
<td>Time since diagnosis yrs</td>
<td>7.2 (7.1)</td>
<td>-</td>
</tr>
</tbody>
</table>

Data are expressed as absolute number or mean, and SD in parenthesis.

Lung function tests

Lung function measurements included forced expiratory volume in one second (FEV1), inspiratory vital capacity (IVC) measured with a pneumotachograph, and total lung capacity (TLC) measured using a body plethysmograph (Compactbody; Jaeger, Würzburg, Germany). The best of three efforts was selected. All volumes were expressed as percentages of the reference values [16].

The transfer factor of the lung for carbon monoxide (TLCO) was measured by the single-breath method (Masterlab; Jaeger, Würzburg, Germany). In order to compare the TLCO level with the quality of life scores, the values were classified into four ranges: 1) normal (±80%); 2) mild decrease (60–80%); 3) moderate decrease (40–60%); and 4) severe decrease (<40% of predicted), according to the American Medical Association classes.

Respiratory muscle strength and respiratory muscle endurance

Inspiratory and expiratory muscle strength were assessed by measuring maximal respiratory mouth pressures using the method of Black and Hyatt [17]. Maximal inspiratory mouth pressure (Pl,max) was measured at residual volume (RV), whilst maximal expiratory mouth pressure (Pemax) was measured at total lung capacity (TLC). The equipment used was a pressure transducer (model MP 45-30; Validyne Engineering Corp., Northridge CA, USA). All signals were recorded on a strip chart (type BD 31; Kipp & Zonen, Delft, The Netherlands). A needle was placed in the proximal end of the mouthpiece to ensure that efforts were performed with open glottis. At least five manoeuvres were performed, until the three highest values were within 5% of each other. All subjects were seated in the upright position and were wearing a noseclip while performing the tests, and the same instructions were given to each subject by one investigator. Values are expressed in absolute terms and as percentages of predicted values according to Wilson et al. [18].

Respiratory muscle endurance was assessed by measuring the endurance time using a modified threshold loading device as designed by Nickerson and Keens [19]. This device has an inspiratory valve, which can be occluded by a weighted plunger. The plunger can be adjusted externally so that patients must generate enough inspiratory pressure to lift the inspiratory valve and allow inspiratory flow. Expiration can be performed without any resistance. The threshold loading device was first tested and validated in healthy subjects before use. There was a very close relationship between the inspiratory pressure (Pl) generated and external weight (W) (Pl=(−0.201126×W + 7.4659); r=0.999, p<0.001; Pl in cmH₂O, W in g). The respiratory muscle endurance time was defined as the maximal time (in seconds) during which a subject could sustain breathing against an inspiratory pressure load equal to 70% of his/her individual Pl,max [20]. All subjects first warmed up by breathing against an inspiratory pressure load equal to 15% of their Pl,max during 2 min. Next they were presented with their individual test load and instructed to breathe for
as long as they could, until they became so tired they could not continue or until they were unable to get enough air. The test was terminated if the respiratory muscle endurance time exceeded 15 min. During the test, the inspiratory pressure was recorded constantly on the strip chart as described.

Peripheral muscle strength

Quadriceps force was measured on the nondominant side with the subject sitting, both hip and knee in 90° flexion, the ankle connected to measuring-equipment based on strain gauges. A nonstretching-band was placed around the hip to prevent the subject from lifting up whilst pulling away the lower leg. The force of the hand muscles was also measured on the nondominant side with the subject sitting, the forearm and hand in a direct line with each other and resting on a table, and the fingers enclosing two wooden handles connected to the measuring equipment based on strain gauges. In both tests, at least three isometric contractions were performed until the differences were not more than 5%. Between each effort there was an interval of 1 min. Values are expressed as kilogram force (kgf).

Health status questionnaire

Health status and quality of life were assessed with the SIP (Dutch version) [15, 21]. The SIP was designed to assess sickness-related behavioural dysfunction. It provides summary scores for physical, psychosocial, and overall behavioural dysfunction, as well as separate scores for 12 categories of activity. The scores are expressed as percentages of the maximal possible score of dysfunction in that particular category or set of categories [22]. The scores range between 0 and 100. The higher the scores, the stronger the impact of the disease on the individual's life.

Statistical analysis

The data of the control subjects and patients were compared using Student's t-test for binominal values and Chi-squared test for ordinal values. Differences in personal characteristics were assessed using Chi-squared tests for categorical data and Student's t-tests for continuous data. Correlation among variables was assessed by single regression analysis. Because of the large number of correlations examined, a p-value of less than 0.01 was considered to be statistically significant. All analyses were performed using the Statistical Package for Social Sciences (SSPS).

Results

Tables 2 and 3 summarize the results of the SIP scores, and the lung function tests, respiratory and peripheral muscle strength assessments, respectively.

The total SIP scores for the patient group were significantly higher compared with the control subjects. In the patients with sarcoidosis, the subscores were significantly higher in the subscales "alertness behaviour", "home management", "recreation and pastimes", "sleep and rest", "social interaction" and "employment" (table 2).

Only one of the 18 patients had a slightly decreased $T_{L,CO}$. The absolute values for FEV1 and $T_{L,CO}$ pred were within the normal range for all patients, as also were the VC and TLC. However, FEV1 % pred was lower in the patients than in the control subjects.

### Table 2. – Average Sickness Impact Profile (SIP) scores for the sarcoidosis patients and a general Dutch population

<table>
<thead>
<tr>
<th>SIP Category</th>
<th>Sarcoidosis patients (n=18)</th>
<th>Control subjects (n=594)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alertness behaviour</td>
<td>9.9 (20.7)**</td>
<td>4.6 (12.4)</td>
</tr>
<tr>
<td>Ambulation</td>
<td>4.1 (8.4)</td>
<td>3.0 (7.8)</td>
</tr>
<tr>
<td>Body care and movement</td>
<td>1.7 (3.8)</td>
<td>1.9 (5.0)</td>
</tr>
<tr>
<td>Communication</td>
<td>2.5 (4.3)</td>
<td>1.1 (4.5)</td>
</tr>
<tr>
<td>Eating</td>
<td>1.1 (3.4)</td>
<td>1.0 (3.2)</td>
</tr>
<tr>
<td>Emotional behaviour</td>
<td>5.7 (12.3)</td>
<td>4.0 (10.0)</td>
</tr>
<tr>
<td>Home management</td>
<td>6.9 (11.3)**</td>
<td>4.8 (11.8)</td>
</tr>
<tr>
<td>Mobility</td>
<td>2.9 (5.6)</td>
<td>2.4 (7.6)</td>
</tr>
<tr>
<td>Recreation and pastimes</td>
<td>10.5 (15.8)**</td>
<td>7.6 (14.1)</td>
</tr>
<tr>
<td>Sleep and rest</td>
<td>14.3 (16.9)**</td>
<td>4.8 (8.2)</td>
</tr>
<tr>
<td>Social interaction</td>
<td>14.0 (23.5)**</td>
<td>4.0 (8.4)</td>
</tr>
<tr>
<td>Employment</td>
<td>12.4 (18.8)**</td>
<td>7.3 (20.0)</td>
</tr>
<tr>
<td>Physical dimension</td>
<td>2.6 (4.4)</td>
<td>2.2 (5.4)</td>
</tr>
<tr>
<td>Psychosocial dimension</td>
<td>11.7 (18.6)**</td>
<td>3.5 (7.2)</td>
</tr>
<tr>
<td>Total SIP score</td>
<td>8.0 (9.7)**</td>
<td>3.4 (5.6)</td>
</tr>
</tbody>
</table>

Data are expressed as mean, and sd in parenthesis. The score are on a scale ranging 0-100. **: p<0.01, sarcoidosis patients versus controls (Student's t-test).

### Table 3. – Lung, respiratory and peripheral muscle function of patients and control subjects

<table>
<thead>
<tr>
<th>Category</th>
<th>Sarcoidosis patients (n=18)</th>
<th>Control subjects (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVC % pred</td>
<td>99 (11)</td>
<td>105 (12)</td>
</tr>
<tr>
<td>FEV1 L</td>
<td>3.1 (0.9)</td>
<td>3.6 (0.7)</td>
</tr>
<tr>
<td>FEV1 % pred</td>
<td>92 (10)**</td>
<td>106 (12)</td>
</tr>
<tr>
<td>$T_{L,CO}$ % pred</td>
<td>86 (9)</td>
<td>100 (8)</td>
</tr>
<tr>
<td>$T_{L,CO}$ normal/decreased</td>
<td>17/1</td>
<td>18/0</td>
</tr>
<tr>
<td>$P_l$,max (at RV) $cm^3$HgO</td>
<td>-86.8 (28.7)**</td>
<td>-112.8 (248)</td>
</tr>
<tr>
<td>% pred</td>
<td>96 (27)**</td>
<td>130 (28)</td>
</tr>
<tr>
<td>$P_{E, max}$ (at TLC) $cm^3$HgO</td>
<td>91.6 (31.5)**</td>
<td>126.1 (34.8)</td>
</tr>
<tr>
<td>% pred</td>
<td>74 (19)**</td>
<td>107 (20)</td>
</tr>
<tr>
<td>Respiratory muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endurance test completed n</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Endurance time s</td>
<td>756 (246)**</td>
<td>869 (130)</td>
</tr>
<tr>
<td>Quadriceps force kgf</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>43.1 (14.1)</td>
<td>45.4 (9.1)</td>
</tr>
<tr>
<td>Female</td>
<td>25.6 (8.4)</td>
<td>32.5 (4.8)</td>
</tr>
<tr>
<td>Hand muscle force kgf</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48.5 (12.8)</td>
<td>52.1 (8.6)</td>
</tr>
<tr>
<td>Female</td>
<td>23.1 (6.8)</td>
<td>33.5 (5.4)</td>
</tr>
</tbody>
</table>

Data are expressed as absolute number or mean, and sd in parenthesis. IVC: inspiratory vital capacity; % pred: percentage of predicted value; FEV1: forced expiratory volume in one second; $T_{L,CO}$: transfer factor of the lung for carbon monoxide; $P_l$,max: maximal inspiratory mouth pressure; RV: residual volume; $P_{E, max}$: maximal expiratory mouth pressure; TLC: total lung capacity. **: p<0.01, sarcoidosis patients versus controls (Student's t-test).
Table 4. - Univariate regression analyses between Sickness Impact Profile (SIP) scores of patients with sarcoidosis and respiratory muscle strength, endurance time and peripheral muscle strength

<table>
<thead>
<tr>
<th>Mobility</th>
<th>$P_{l,max}$</th>
<th>$P_{E,max}$</th>
<th>Endurance time</th>
<th>HMF</th>
<th>QF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body care and movement</td>
<td>$-0.30$</td>
<td>$-0.07$</td>
<td>$-0.79$</td>
<td>$0.17$</td>
<td>$0.22$</td>
</tr>
<tr>
<td>r</td>
<td>$-0.30$</td>
<td>$-0.07$</td>
<td>$&lt;0.001$</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>p-value</td>
<td>NS</td>
<td>NS</td>
<td>$&lt;0.001$</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

HMF: hand muscle force; QF: quadriceps force; NS: non-significant. For further definitions see legend to table 3.

Muscle weakness is a condition in which the capacity for a rested muscle to generate force is decreased [23]. On the other hand, the observation and measurement of a decreased respiratory muscle strength, as described by the SIP scores of patients with sarcoidosis, indicates an inspiratory weakness and fatigue. Moreover, in the present study, the $P_{E,max}$ was significantly lower than in normal controls [14].

The results of the present and previous studies, therefore, suggest that $P_{l,max}$ and $P_{E,max}$ are related to functional impairment due to sarcoidosis. These results also emphasize the need for an integrative approach in the assessment and therapeutic management of sarcoidosis. It should be noted, however, that the respiratory muscle tests applied in the present study depend on the cooperation of the patient. To the best of our knowledge, nonvolitional tests of respiratory muscle function, such as magnetic or electrical stimulation of the phrenic nerves, have not been reported in these patients.

Peripheral muscle strength, i.e. quadriceps and hand muscle force, showed no differences between the sarcoidosis patients and control subjects (table 3).

The respiratory muscle endurance time correlated with the SIP subscales "mobility" ($p<0.01$) and "body care and movement" ($p<0.001$). However, no correlations were found between the SIP scores and $P_{l,max}$, $P_{E,max}$ and peripheral muscle strength, respectively (table 4). Patients with symptoms (n=7) (table 1) showed lower $P_{l,max}$ ($p<0.03$) and respiratory muscle endurance time ($p<0.005$), while patients who experienced fatigue (n=6) had a lower $P_{E,max}$ ($p<0.03$) compared to those without complaints.

The radiographic stage was related to the SIP subscales "alertness behaviour" ($p<0.001$), "emotional behaviour" ($p<0.001$), "home management" ($p<0.005$) and "social interaction" ($p<0.001$). The duration of disease, the FEV1, and the sACE levels showed no relationship with percentile scores of any of the subscales. Furthermore, no relationship between radiographic stage, sACE, respiratory muscle strength, and respiratory muscle endurance time were found.

Discussion

This study has shown that respiratory muscle strength and respiratory muscle endurance are reduced in patients with sarcoidosis. Patients with the symptom of fatigue had significantly lower maximum expiratory pressures than those without symptoms. A decreased respiratory muscle endurance time suggests the presence of respiratory muscle fatigue. Muscle fatigue has been defined as a condition in which there is a reduction in the capacity for developing force and/or velocity of a muscle in response to a load, and is reversible by rest [23]. In general, muscle fatigue occurs whenever energy demand exceeds energy supply [24]. Applying this to respiratory muscles, fatigue occurs when these muscles work under conditions where there is an imbalance between energy demand and supply [24].
sarcoidosis are secondary to the direct effect of the ac-
cumulation of activated immunocompetent cells in the
involved tissues, notably helper T-lymphocytes and mac-
rophages, and by an increased production of different
cytokines [28, 29]. These cytokines appear to be pro-
duced in inflamed lesions of sarcoidosis and released
into the bloodstream [30]. Future identification of these
products could lead to specific therapeutic interventions
aimed at blocking their effect in the clinical manage-
ment of patients with inflammatory disorders, such as
sarcoidosis.

As previously suggested, impaired respiratory muscle
function suggests that the respiratory muscles can be
involved in the granulomatous process of sarcoidosis [13].
Many reports have described granulomatous myopathy
without overt manifestations of sarcoidosis elsewhere;
sometimes a past history of sarcoidosis was suggested.
Hence, granulomas in muscles may persist after those
in other organs have become inactive or have resolved
in patients who have passed through the active gener-
alized stages of sarcoidosis without obvious symptoms
[31]. Little is known about involvement of respiratory
muscles, as only a few cases have been described [14,
32, 33]. For example, it is not known whether diap-
hragm and/or intercostal muscle involvement in sar-
coidosis is a possible contributory factor to dyspnoea or
improvement of vital capacity [31]. However, histologi-
cal confirmation of respiratory muscle involvement is
hard to obtain. Furthermore, myopathy, including disor-
ders of the respiratory muscles, is a well-known side-
effect of corticosteroids [34, 35]. It should be considered
especially with higher doses of steroids, in the presence
of markedly impaired respiratory muscle strength or con-
tinuous treatment with fluorinated steroids [36]. In the
present group of patients, only seven had been treated
with steroids during the 3 months prior to the study and
the doses they received were low. Moreover, the respi-
ratory and peripheral muscle strength did not differ
between patients with or without a history of corticos-
teroid treatment.

The TLCO is considered by some authors to be the
most sensitive index of lung function in sarcoidosis. It
is often the first or only index to be decreased [14].
Remarkably, however, in the present study the respi-
ratory muscle force and endurance were significantly
lower than in the control group, even though other lung
function tests were normal. This suggests that maximal
mouth pressure and respiratory muscle endurance time
may be more sensitive to functional impairment due to
sarcoidosis than are the TLCO or VC, which have been
suggested as the best indices to correlate with working
capacity [37]. The relationship between radiographic
stage, lung function and exercise abnormality have, how-
ever, been variable [38]. Clearly, there is a wide spectrum
of tissue inflammation and organ dysfunction within, as
well as between, each radiographic stage. KARETZKY
and MCDONOUGH [38] found that the magnitude of func-
tional impairment may vary widely from the apparent
histopathological involvement as reflected by chest
radiography and lung volumes. In the present study, we
found a relationship between the radiographic stage and
impairment in the fields "alertness behaviour", "emo-
tional behaviour", "home management" and "social inter-
action".

Furthermore, in the present study, the SIP subscales
"mobility" and "body care and movement" as well as the
presence of symptoms were shown to correlate with res-
piratory muscle endurance time. However, for both of
these latter domains there was no difference between
patients and the control subjects. Moreover, our results
show that patients with sarcoidosis are limited in phys-
ical and psychosocial functioning. They appear to be
particularly affected in the fields "sleep and rest", "re-
creation and pastime", "employment", "alertness beha-
viour", "home management" and "social interaction",
compared to a control group [15]. This diversity illus-
trates the broad impact of sarcoidosis on patients' quality
of life.

In conclusion, respiratory muscle strength and endur-
ance are reduced in patients with sarcoidosis. Decreas-
ed respiratory muscle endurance was found to be related
particularly to the Sickness Impact Profile subscales
"mobility" and "body care and movement". However, no
such relationship was found between these latter Sick-
ness Impact Profile subscales and routinely performed lung
function tests, such as transfer factor and spirom-
etry. Measuring respiratory muscle function seems to
quantify and characterize the functional impairment in
patients with sarcoidosis and reflects symptoms, such as
fatigue and general weakness, that are otherwise dif-
ficult to assess objectively. Therefore, we suggest that
measurements of respiratory muscle strength and endur-
ance time could be usefully included in the diagnostic
work-up and follow-up of patients with sarcoidosis. Fur-
ther studies are needed to assess respiratory and peri-
pheral muscle involvement, as well as the relationship
with the presence of inflammatory characteristics in sar-
coidosis.

Acknowledgements: The authors would like to thank
H.M. Jacob for providing the Dutch SIP control data,
M.D.P. Elfferich and L.M.M. Kock for their great help
in collecting the data and their advice. Furthermore, they
would like to thank Ch. van der Grinten and G. Vissers
for technical advice, J. de Vries for statistical assistance,
and the lung function laboratory workers, in particular
L. van de Pol, for technical assistance and advice.

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