Pulmonary Manifestations of Uncomplicated Falciparum and Vivax Malaria: Cough, Small Airways Obstruction, Impaired Gas Transfer, and Increased Pulmonary Phagocytic Activity

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Despite recognition of acute respiratory distress syndrome in both falciparum and vivax malaria, disease-related changes in pulmonary function have not been defined, and underlying mechanisms are not well understood. Respiratory symptoms, pulmonary function, pulmonary phagocytic cell activity, and longitudinal changes were examined in 26 adults with uncomplicated falciparum, vivax, and ovale malaria after treatment. Self-limiting cough occurred in both falciparum (36%) and vivax or ovale (53%) malaria. In infection with each malaria species, admission measures of airflow and gas transfer were lower than predicted, and mean lung 99mtechnetium-sulfur-colloid uptake was significantly increased. Changes were most evident in falciparum malaria, with treatment resulting in initial worsening of airflow obstruction and gas transfer. Altered pulmonary function in malaria is common and includes airflow obstruction, impaired ventilation, impaired gas transfer, and increased pulmonary phagocytic activity, and its occurrence in both vivax and falciparum malaria suggests that there may be common underlying immunological mechanisms.

Respiratory symptoms and signs are common in uncomplicated Plasmodium falciparum malaria, particularly in African children [1, 2]. In these children, there is considerable clinical overlap with the features of pneumonia [1, 2]. In adults, respiratory symptoms and signs also occur in uncomplicated falciparum malaria, with a reported frequency of 4%–18% [3–8]; however, in some early studies, the denominator was unclear, accuracy of speciation was not ensured, radiology was often lacking, and secondary bacterial infections were included. Respiratory findings are also a major feature in severe malaria. In African children, respiratory distress is an important risk factor for fatal outcome. Metabolic acidosis is a major cause of respiratory distress in these children [9–12], but pneumonitis from the sequestered parasitized red blood cells and inflammatory cells seen in postmortem pulmonary microvasculature [13, 14] may also contribute to respiratory distress. In adults, noncardiogenic pulmonary edema and acute respiratory distress syndrome (ARDS) with normal pulmonary artery occlusion pressure are grave complications of falciparum malaria, with a high mortality rate. They are also a major cause of death in those adults who present with other manifestations of severe malaria [4, 15–17]. In some patients, ARDS is present at admission and is associated with high parasitemia [15]; however, in many instances, ARDS commences 1–5 days after treatment has begun, when peripheral parasitemia has decreased or disappeared [4, 18, 19]. The timing is similar to that of ARDS occurring with bacterial sepsis [20] and that of the flare in respiratory distress occurring after commencement of antimicrobial therapy for Pneumocystis carini, which suggests that there may be a similar inflammatory pathology in falciparum malaria.

Until recently, it was thought that vivax malaria did not cause pulmonary complications; however, there are now 8 reported cases of ARDS occurring after commencement of therapy for Plasmodium vivax malaria [21–28] and 1 case of ARDS complicating Plasmodium ovale malaria [29]. Microvascular sequestration of parasitized red blood cells is thought to be the pathophysiological mechanism underlying most extrapulmo-

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Written informed consent was then obtained. Total radiation dose in all patients and control subjects was less than the 5 mSv limit for medical research recommended by NHMRC guidelines and the South Australian Health Commission and complied with the 1978 Northern Territory Radiation Safety Control Act.

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nary organ-specific manifestations of severe falciparum malaria. Red blood cells parasitized with *P. vivax* or *P. ovale* do not cy-toadhere to endothelial cells [19], so the occurrence of ARDS in vivax malaria suggests that lung injury in malaria is not caused solely by microvascular sequestration of parasitized red blood cells. The vivax malaria ARDS cases have also reawakened interest in reports of respiratory symptomatology in uncomplicated vivax malaria found in the early malaria literature [5, 8].

There have been few autopsy series or reports with detailed descriptions of pulmonary histopathology in falciparum malaria [3, 4, 13, 14, 30, 31]. Sequestered parasitized red blood cells are found in alveolar capillaries, but, in contrast to the mature stages found in other organs, these are more frequently rings and trophozoites. Of note, large numbers of intravascular mononuclear cells have been found in some of these autopsy studies [13, 14, 30]. Increased pulmonary phagocytic cell activity has also been documented in single case reports in uncomplicated falciparum and vivax malaria [32, 33].

Despite clinical recognition of pulmonary manifestations in both uncomplicated and severe malaria, disease-related changes in pulmonary function have not been defined, and underlying mechanisms are not well understood. We, therefore, prospectively examined pulmonary phagocytic cell activity, underlying changes in pulmonary function, and longitudinal changes in response to treatment in uncomplicated *P. falciparum*, *P. vivax*, and *P. ovale* malaria.

**Patients and Methods**

*Patients and study site.* Subjects were inpatients at Royal Darwin Hospital and Darwin Private Hospital (Darwin, Northern Territory [NT], Australia) with a microscopy-confirmed diagnosis of uncomplicated malaria [19] during 1999–2000. Malaria is no longer endemic in northern Australia; however, the tropical northern area of the NT remains malaria receptive [34]. For this reason, NT public health policy to prevent reintroduction of malaria required that all parastemic patients be admitted to the hospital until clearance of asexual stage parasitemia and administration of therapy to sterilize gametocytes. Eligible subjects were adults with fever or a history of fever and *P. falciparum*, *P. vivax*, or *P. ovale* parasites seen on Giemsa-stained thick blood film examination. Patients <18 or >75 years old, pregnant or lactating women, prisoners, and those unable to give informed consent were excluded. All thick blood film diagnoses were cross-checked by a referral center microscopist with >20 years’ experience. Histidine-rich protein 2 antigen was detected by immunochromatographic antigen testing (ICT Pf/Pv; Binax) [35] in all cases of *P. falciparum* but in no cases of *P. vivax* or *P. ovale* infection. Falciparum malaria was treated with quinine plus doxycycline, or primaquine, and vivax and ovale malaria were treated with chloroquine, followed by 14 days of primaquine [36]. In contrast to the well-established normal values for pulmonary function tests, normal values for technetium lung uptake are not well defined. We thus selected control subjects for technetium-sulfur-colloid lung scans from among the investigators; all were nonsmokers with no history of lung disease.

**Serial clinical and pulmonary function assessment.** Clinical assessments and tests of pulmonary function were performed at admission, daily until thick blood films were negative, and again at postdischarge review, 7–14 days after admission. Clinical assessments included respiratory signs and symptoms, hemoglobin (Hb) concentration measured with a Coulter counter, and parasite count by Giemsa-stained thick blood film. Cough was recorded as being present on the basis of patient history (either volunteered or elicited in response to direct questioning), with or without observed cough. Chest X rays were taken at admission.

Pulmonary function was assessed using an Elite DL combined pulmonary function testing station (Medical Graphics) for spirometry, gas transfer, and plethysmographic lung volume assessment. Intra-subject variability and technique were assessed using American Thoracic Society criteria [37]. Spirometry included forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and forced expiratory flow from 25%–75% of expired volume (FEF25–75%). Reversibility was assessed using 200 µg of salbutamol via metered dose inhaler, with measurements repeated after 2 min. Normal values for measures of pulmonary function were calculated from predicted equations on the basis of height, weight, age, and sex, corrected for race as appropriate [38, 39]. Diffusing capacity (DLCO) was measured using the single breath apeana method (DLCO SB) [40, 41], with corrections for Hb and alveolar volume (VA) measured by the single breath diffusion technique (DLCO SB/VA [Hb corrected]) [40, 41]. Subdivisions of lung volume were determined using body plethysmography. In combination with spirometry, residual volume (RV) and thoracic gas volume (TGV) were calculated. Because these measurements do not rely on the diffusion of inspired gas, as does total lung capacity (TLC) determined by helium diffusion, they include areas of the lung that do not communicate with the rest of the conducting airways. Thus, changes in TLC:VA over time, compared with changes in TGV, can be inferred to represent the effect of poor ventilation secondary to small airway pathology.

**Pulmonary phagocytic activity.** Pulmonary phagocytic cell activity was assessed using technetium-sulfur-colloid scans with lung views. Lung uptake with these scans is usually <1% [42]. technetium-sulfur-colloid is phagocytosed by pulmonary phagocytic cells; therefore, lung gamma activity is a measure of phagocytic activity and/or phagocytic cell counts, particularly monocytes and macrophages [43–47]. Scans were performed on day 1 or 2, and, for 7 patients, day 3 uptake was compared with day 1 uptake. Malaria and control scans were assessed independently by 2 experienced nuclear physicians, each unaware of diagnosis and subject status. Lung uptake was scored as follows: 0, none visible above background; 1, some ill-defined lung activity demonstrated; 2, lung uptake seen with a relatively photopenic cardiac defect or void; and 3, clearly visible cardiac photopenic defect or void. Bone marrow uptake was scored as follows: 0, no discrete bone marrow activity seen; 1, vertebrae identified; 2, sternum, ribs, and scapulae visible; and 3, marked, extreme bone marrow activity.

**Pulmonary clearance of aerosolized technetium–diethylenetriaminepentaacetate (DTPA).** Changes in alveolar epithelial permeability were assessed by measuring clearance of aerosolized technetium-DTPA. Increased isotope technetium-DTPA clearance is a sensitive measure of
loss of alveolar epithelial tight junction integrity in conditions such as ARDS [48–50]. Clearance is also increased in smokers [48–50]. Measurements were performed on days 1, 3, and 5 and 1 week after discharge.

Statistical analysis. Statistical analysis was performed using Intercooled Stata (version 7.0 for Windows; StataCorp). Data are presented as means or medians, when data did not follow a normal distribution. Comparisons of unpaired and paired continuous variables were performed using Student’s t test or by the Wilcoxon rank sum test or by the matched-pairs signed-rank test for nonparametric data. Dichotomous variables were compared using the χ² or Fisher’s exact test.

Results

Twenty-six patients with uncomplicated symptomatic malaria were studied (table 1). One patient had infection with P. ovale. Because this parasite has a life cycle and clinical course that is similar to P. vivax, this patient was grouped with the patients with vivax malaria. All patients had recent history of fever, with 55% of patients with falciparum and 87% of patients with vivax having fever at presentation. All had relatively low parasitemia. None had manifestations of severe malaria [19], and all made an uncomplicated recovery. Except for 3 patients with a distant history of asthma, no underlying lung or liver disease was present. Patients with P. vivax infection were younger than those with P. falciparum but otherwise had similar characteristics. All had been residents of a nonmalarious region for ≥ 1 year prior to short-term travel to a malarious area. Most had not taken antimalarial treatment or prophylaxis in the preceding month. Although half had a previous episode of malaria, the most recent occurred a median of 2 years (range, 0.2–30 years) prior to the study, which is consistent with a lack of significant preexisting immunity. Respiratory symptoms were frequent, occurring in nearly half the patients with malaria. Recent-onset cough was found in 36% and 53% of patients with P. falciparum and P. vivax, respectively, and resolved in all of them (figure 1, bottom). No crackles or wheezes were heard on auscultation. Cough was not present prior to malaria in any patient, was mostly nonproductive, and was no more common in smokers (56%) than nonsmokers (41%; P = .48). Admission and convalescent (≥ 7 days after discharge) values for spirometry, gas transfer, and lung volume variables, as a proportion of predicted values (except for the FEV₁ : FVC ratio), are presented in table 2. In general, patients with malaria demonstrated lower admission values for lung function variables than those predicted. All chest X rays taken at admission were normal.

Measures of airflow obstruction (FEV₁ and FEF25–75) at admission were significantly lower than predicted in patients with P. falciparum infection (P < .05; table 2). The effect of bronchodilators was assessed in 14 of 26 patients. There was no significant effect on FEV₁. Convalescent FEV₁ and FEF25–75 in these patients demonstrated a significant recovery toward predicted values (P = .01) without significant change in the FEV₁ : FVC ratio. Vₐ, in P. falciparum malaria was significantly lower than predicted at admission (P = .02) and returned to normal during convalescence (P = .03). In contrast, TLC and RV were normal at admission and did not change during convalescence. Gas supply difficulties resulted in fewer subjects having gas transfer than other lung function tests. DLCO/VA (Hb corrected) was lower than that predicted at admission for patients with P. falciparum (n = 5) and P. vivax (n = 9) malaria, with means in each group being 73% and 70%, respectively, of those predicted (P = .21 and P = .07, respectively). Adjusted gas transfer was significantly different from predicted when the falciparum and

| Table 1. Demographic characteristics of patients with malaria at presentation, by infecting parasite. |
| Characteristic | Plasmodium falciparum | Plasmodium vivax | Total |
| No. of patients | 11 | 15 | 26 |
| Age, mean years (SD) | 38.1 (14.0) | 29.4 (6.6) | 33.1 (11.0) |
| Male | 82 | 93 | 88 |
| Admission temperature, median °C (range) | 37.5 (35.6–40.2) | 38.6 (36.3–40.2) | 38.4 (35.6–40.2) |
| Hemoglobin level, mean g/L (SD) | 13.4 (2.7) | 13.3 (1.8) | 13.3 (2.2) |
| Tobacco smoker | 27 | 40 | 35 |
| Parasitemia, geometric mean parasites/µL (range) | 4364 (200–47,000) | 1765 (100–22,000) | 2574 (100–47,000) |
| Cough | | | |
| Dry | 27 | 40 | 35 |
| Productive | 9 | 13 | 12 |
| Any | 36 | 53 | 46 |
| Antimalarials within last month | 9 | 47 | 31 |
| History of asthma | 18 | 7 | 12 |
| History of malaria | 45 | 60 | 54 |

NOTE. Data are percentage of patients, except where noted.

*Includes one subject with P. ovale infection.

*Patients with P. vivax infection were younger than those with P. falciparum infection (P = .045), but there were no significant differences between species for other characteristics.
vivax malaria groups were combined as “any malaria” ($P = .025$).
There was no significant improvement in measures of gas transfer 7–14 days after admission, although, in $P. falciparum$ malaria, gas transfer fell further after initiation of treatment (figure 1, bottom).

As with $P. falciparum$ malaria, admission FEV$_1$ and FEF$_{25–75}$ values were also significantly lower than predicted in patients with $P. vivax$ malaria ($P < .05$). $V_A$ was impaired but was not significantly different from predicted values ($P = .07$). Overall measures of airflow, gas transfer, and lung volume in $P. vivax$ infection were not markedly impaired at admission, and, although convalescent values were, in general, higher and closer to predicted values, the longitudinal improvements were not statistically significant. For both Plasmodium species, admission airflow obstruction and gas transfer impairment were similar in smokers and nonsmokers and in those with and without a history of asthma (data not shown). The patient with $P. ovale$ had similar admission features as patients with $P. vivax$, with cough, evidence of airflow obstruction (FEV$_1$, 74% of predicted; FEF$_{25–75}$, 55% of predicted), mildly reduced $V_A$ (91% of predicted), impaired gas transfer (DL$_{CO}$/SB/$V_A$ [Hb corrected], 85% of predicted), and increased lung scan uptake (score, 2.5).

Longitudinal changes in parasite count and pulmonary function after initiation of treatment are shown in figure 1. Patients with $P. vivax$ infection had faster parasite clearance than those with $P. falciparum$ infection, with significantly more patients with $P. vivax$ infection having parasite clearance, as determined by thick blood film, at day 3 ($P < .05$) and day 4 ($P < .001$) post-admission (figure 1, top). In falciparum malaria, a number of initially impaired parameters worsened during the first 1–3 days of treatment (figure 1, bottom), including gas transfer, which, by days 14–18, had returned to admission levels only, not to predicted levels. Follow-up later in convalescence to test for a return to predicted level was not possible. Measures of airflow obstruction also worsened after initiation of treatment before improving in convalescence (figure 1, bottom).

Twenty-one subjects consented to $^{99m}$Tc-sulfur-colloid lung scans—9 patients with $P. falciparum$ infection, 8 patients with $P. vivax$ infection, and 4 control subjects. All lung scans were technically adequate, and none was excluded from analysis.
The day 3 bone marrow uptake score was also no different from reduced increase in pulmonary phagocytic cell numbers or activity. The occurrence of lung function impairment in both vivax and falciparum malaria suggests that there are common underlying inflammatory mechanisms. These mechanisms may be occurring with greater magnitude in severe malaria, where lung injury is a major cause of mortality in non-immune adults.

Subclinical impairment of lung function was common in falciparum, vivax, and ovale malaria, with small airways obstruction, impaired alveolar ventilation, reduced gas transfer, and increased pulmonary phagocytic activity. The occurrence of lung function impairment in both vivax and falciparum malaria suggests that there are common underlying inflammatory mechanisms. These mechanisms may be occurring with greater magnitude in severe malaria, where lung injury is a major cause of mortality in non-immune adults.

Impaired admission values for FEV₁ indicate airflow obstruction in malaria. They are unlikely to reflect consistently poor forced expiratory maneuvers by patients who are ill with malaria, because flows were also reduced in the middle of forced expiration, as assessed by FEF₂₅₋₇₅, which is less effort dependent [51]. The lack of a significant reduction in TGV and the reduced admission VA suggest that the reduction in FVC was not due to reduced lung volume but rather to impaired alveolar ventilation from small airways obstruction. Our findings are consistent with

### Table 2. Lung function in malaria patients at baseline and in convalescence (≥7 days after admission), by infecting parasite.

<table>
<thead>
<tr>
<th>Measure of lung function</th>
<th>Plasmodium falciparum</th>
<th>Plasmodium vivax&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>Baseline value</td>
<td>Convalescent value</td>
</tr>
<tr>
<td>FEV₁</td>
<td>0.79 (0.04)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.89 (0.03)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>FVC</td>
<td>0.86 (0.03)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.95 (0.03)</td>
</tr>
<tr>
<td>FEV₁:FVC&lt;sup&gt;c&lt;/sup&gt;</td>
<td>76 (3)</td>
<td>77 (3)</td>
</tr>
<tr>
<td>FEF&lt;sub&gt;25–75&lt;/sub&gt;</td>
<td>0.59 (0.06)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.71 (0.07)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>V&lt;sub&gt;ₕ&lt;/sub&gt;</td>
<td>0.86 (0.03)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.96 (0.02)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>DL&lt;sub&gt;CO&lt;/sub&gt;S&lt;sub&gt;B&lt;/sub&gt;/VA&lt;sub&gt;ₕ&lt;/sub&gt;</td>
<td>Hb corrected</td>
<td>0.73 (0.07)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>TLC</td>
<td>0.96 (0.04)</td>
<td>1.02 (0.05)</td>
</tr>
<tr>
<td>RV, L</td>
<td>1.14 (0.14)</td>
<td>1.20 (0.17)</td>
</tr>
</tbody>
</table>

NOTE. Data are percentage (SE) of predicted values. Comparisons between admission and convalescent values were done by 1-sided paired Student’s t test. DL<sub>CO</sub>S<sub>B</sub>/VA<sub>ₕ</sub>, Hb corrected, diffusing capacity measured using the single breath apnea method with corrections for hemoglobin and alveolar volume; FEF<sub>25–75</sub>, forced expiratory flow of 25%–75% of expired volume; FEV<sub>₁</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; NS, not significant; RV, residual volume; TLC, total lung capacity; V<sub>ₕ</sub>, alveolar volume.

<sup>a</sup>Includes 1 patient with <i>P. ovale</i> infection.

<sup>b</sup>Indicates parameters significantly lower than predicted (<i>P</i> < .05).

<sup>c</sup>Presented as raw ratios.

<sup>d</sup>Admission DL<sub>CO</sub>S<sub>B</sub>/VA<sub>ₕ</sub> was significantly lower than predicted when <i>P. falciparum</i> and <i>P. vivax</i> malaria were combined as “any malaria.”

There was satisfactory agreement among the independent observers, with an <i>k</i> score of 0.64 (<i>P</i> < .0001) and 0.52 (<i>P</i> < .0001) for bone marrow and lung uptake, respectively, and no observer disagreement of >1 grade. The mean age of healthy subjects for control scans was 41.5 years (range, 38–44 years). Lung uptake was increased in both types of malaria, with mean (SD) lung uptake scores of 2.3 (0.7) in <i>P. falciparum</i> infection (100% with uptake score ≥1) and 1.5 (0.8) in <i>P. vivax</i> infection (50% with uptake score ≥1), compared with 0.5 (0.4) in control subjects (<i>P</i> = .019; figure 2). Pairwise comparisons showed significantly higher mean lung uptake scores in <i>P. falciparum</i> infection than in <i>P. vivax</i> infection (<i>P</i> = .03) and in <i>P. falciparum</i> infection versus control subjects (<i>P</i> = .006). Lung uptake in patients with <i>P. vivax</i> infection was also significantly higher than in control subjects (<i>P</i> = .04). In contrast, there were no significant differences among the groups in bone marrow uptake, with mean bone uptake scores of 1.72, 1.68, and 1.0 in patients with <i>P. falciparum</i> and <i>P. vivax</i> infection and in control subjects, respectively. (<i>P</i> = .14). Longitudinal data were available for 7 patients (4 with <i>P. falciparum</i> and 3 with <i>P. vivax</i> infection) who had repeat scans on day 3. Mean lung uptake score on day 3 was not significantly different from day 1 uptake score in patients with either <i>P. falciparum</i> (day 1, 1.88; day 3, 2.0; <i>P</i> = .39) or <i>P. vivax</i> malaria (day 1, 1.0; day 3, 0.83; <i>P</i> = .87), although the number of patients with paired scans was small, and the measure of lung uptake used would not detect a moderate treatment-induced increase in pulmonary phagocytic cell numbers or activity. The day 3 bone marrow uptake score was also no different from that at admission in patients with either <i>P. falciparum</i> (day 1, 2.25; day 3, 2.35; <i>P</i> = .39) or <i>P. vivax</i> malaria (day 1, 2.0; day 3, 2.0; <i>P</i> = 1.00).
early descriptions of bronchitis as the most common respiratory presentation of falciparum malaria [5, 7, 52] and with a previous study showing reduced (albeit effort-dependent) peak expiratory flow rates, wheezing, and exacerbation of preexisting asthma in falciparum malaria [6]. Airflow obstruction in both vivax and falciparum malaria suggests that obstruction does not result solely from microvascular obstruction by parasitized red blood cells in airway vasculature (found only with \textit{P. falciparum}), but likely results from inflammation of small airways.

Both falciparum and vivax/ovale malaria were associated with impaired gas transfer, which, although possibly related to small airway-induced ventilation-perfusion mismatch, more likely reflects subclinical pathology at the alveolar-capillary membrane. This notion is supported by the finding that gas transfer continued to fall as FEF25–75 increased. It is unlikely that airflow obstruction and impaired diffusing capacity in malaria reflect nonspecific effects of any febrile illness [53, 54], because increased temperature does not significantly alter DL_{CO} and lung mechanical properties in humans [54].

It is likely that ARDS, now recognized to occur in both falciparum [4, 15, 16, 55–60] and vivax/ovale [21–29] malaria, is the extreme end of a predominantly subclinical spectrum of alveolar-capillary pathology in malaria [60, 61]. The mechanisms underlying malaria ARDS are not clear. Although necropsy studies of severe falciparum malaria demonstrate alveolar capillary sequestration of parasitized red blood cells [62], these are frequently less-mature stages than those seen in other organs such as the brain [13, 31]. Moreover, intravascular monocytes are seen to a greater degree in alveolar capillaries than in other organ microvasculature [4, 30, 31] and peripheral blood [14]. Similar intravascular monocyte infiltrates also have been reported in hamster models of malaria lung injury [63]. Intravascular neutrophils are also seen [14, 31]. The parallel increases in pulmonary phagocytic activity and impaired gas transfer

Figure 2. Representative 99mtechnetium-sulfur-colloid lung scans. A. Markedly increased pulmonary phagocytic activity is seen in \textit{Plasmodium falciparum} malaria (mean [SD] lung uptake score, 2.3 [0.7]). Moderate increase is seen in \textit{P. vivax} malaria (mean lung uptake score, 1.5 [0.8]; B) and \textit{P. ovale} malaria (mean lung uptake score, 2.5; C), relative to healthy control subjects (mean lung uptake score, 0.5 [0.4]; D; \(P = .019\)). Pairwise comparisons showed significantly higher mean lung uptake scores in patients infected with \textit{P. falciparum} than those infected with \textit{P. vivax} (\(P = .03\)), in patients infected with \textit{P. falciparum} vs. control subjects (\(P = .006\)), and in patients infected with \textit{P. vivax} vs. control subjects (\(P = .04\)).
suggest that a similar pulmonary accumulation of intravascular monocytes occurs in uncomplicated malaria, possibly resulting in subclinical endothelial injury. It was notable that gas transfer, as measured by DLCO, was impaired, but ⁹⁹ᵐTc-DTPA clearance (an extremely sensitive measure of alveolar epithelial tight junction integrity [48–50]) was not increased. Increased CO diffusion distance and impaired gas transfer may thus result from predominantly vascular rather than alveolar processes, which is consistent with electron microscopy findings in fatal malaria—endothelial swelling, interstitial edema, and adherence of intravascular monocytes to capillary endothelium [14, 30].

Bone marrow Tc uptake was not significantly increased in malaria, suggesting that increased lung uptake cannot be explained by a nonspecific increase in macrophage activity in malaria or by a compensatory increase in uptake from liver disease. We hypothesize that lung monocyte accumulation occurs in vivax and ovale malaria, as well as in falciparum malaria, with intravascular inflammatory changes contributing to impaired gas transfer and respiratory manifestations of vivax malaria. The milder impairment of lung function and lesser frequency of ARDS in vivax malaria may be related to the absence of microvascular sequestration of parasitized red blood cells, less tissue localization of Plasmodium toxin release [64], and, thus, a lesser degree of deleterious microvascular inflammatory responses and ischemia-reperfusion injury [65, 66].

Noncardiogenic pulmonary edema often develops rapidly days after starting antimalarial therapy [19]. Gas transfer in P. falciparum infection decreased after initiation of treatment, suggesting that alveolar-capillary pathology may be exacerbated by a posttreatment inflammatory response, analogous to ARDS after treatment of bacterial sepsis. Lung ischemia-reperfusion injury may occur after antimalarial drug clearance of sequestered parasitized red blood cells and monocytes [65–67] in microvasculature. ARDS in vivax malaria also develops after initiation of treatment, which is consistent with a similar treatment-exacerbated inflammatory process.

It is possible that the anti-inflammatory effects of chloroquine or doxycycline, which are used to a greater extent in patients with P. vivax infection, may have attenuated the pulmonary inflammatory response in patients with P. vivax infection. The patients were mostly young adults, and none had preexisting respiratory symptoms. Moreover, patients acted as their own controls, and longitudinal improvements in lung function thus were unlikely to be due to any preexisting (e.g., smoking related) abnormalities in lung function.

Although modern literature has focused on respiratory manifestations of falciparum malaria, older literature describes respiratory symptoms in uncomplicated adult vivax malaria [5, 8, 68]. We have shown that respiratory manifestations and altered lung function occur during uncomplicated infection with 3 Plasmodium species, with cough occurring in the majority of adults with vivax malaria. Recent studies of Indonesian children show that cough and crackles are at least as common in P. vivax as in P. falciparum infection [69], suggesting that the well-recognized clinical overlap in children between acute respiratory infection and falciparum malaria [1, 2] may also occur with vivax malaria. Although the quality of microscopy cannot be ensured in early reports of respiratory symptoms with quartan malaria (Plasmodium ovale) [70], it is likely that all 4 species can have pulmonary presentations. Increased recognition that respiratory symptoms occur in uncomplicated malaria may prevent delays in diagnosis and treatment.

In summary, altered pulmonary physiology in falciparum, vivax, and ovale malaria includes airflow obstruction, impaired ventilation, reduced gas transfer, and increased pulmonary phagocytic activity. Longitudinal examination of the cellular mechanisms underlying these changes in uncomplicated malaria may provide important insights into the pathophysiology of ARDS and may suggest targets for therapeutic intervention for this largely untreatable complication of severe malaria.

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