Lung Injury in Vivax Malaria: Pathophysiological Evidence for Pulmonary Vascular Sequestration and Posttreatment Alveolar-Capillary Inflammation

Nicholas M. Anstey,1 Tjandra Handojo,1 Michael C. F. Pain,2 Enny Kenangalem,2,5 Emiliana Tjitra,4 Ric N. Price,1,7 and Graeme P. Maguire1,3

1International Health Program, Infectious Diseases Division, Menzies School of Health Research and Charles Darwin University, Darwin; 2Department of Respiratory Medicine, Royal Melbourne Hospital and University of Melbourne, Melbourne; and 3Western Australia Country Health Service–Kimberley, Broome, Australia; 4National Institute of Health Research and Development–Menzies School of Health Research Timika Research Program, Mitra Masyrakat Hospital, and 5Ministry of Health, Mimika District, Timika, Papua, and 6National Institute of Health Research and Development, Ministry of Health, Jakarta, Indonesia; 7Centre for Vaccinology and Tropical Medicine, Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford, United Kingdom

Background. The mechanisms underlying lung injury in vivax malaria are not well understood. Inflammatory responses to Plasmodium falciparum and P. vivax, to our knowledge, have not previously been compared at an organ level.

Methods. Respiratory symptoms and physiological aspects were measured longitudinally in Indonesian adults with uncomplicated vivax (n = 50) and falciparum (n = 50) malaria. Normal values were derived from 109 control subjects. Gas transfer was partitioned into its alveolar-capillary membrane (Dm) and pulmonary capillary vascular (Vc) components, to characterize the site and timing of impaired gas transfer.

Results. Mean baseline Vc volume was significantly reduced in vivax and falciparum malaria, improving with treatment in each species. Baseline Dm function was not impaired in either species. The progressive deterioration in Dm function after treatment was statistically significant in vivax malaria but not in uncomplicated falciparum malaria. Oxygen saturation deteriorated after treatment in vivax but improved in falciparum malaria.

Conclusions. The baseline reduction in Vc volume but not in Dm function suggests encroachment on Vc volume by parasitized erythrocytes and suggests that P. vivax–infected erythrocytes may sequester within the pulmonary microvasculature. Progressive alveolar-capillary dysfunction after treatment of vivax malaria is consistent with a greater inflammatory response to a given parasite burden in P. vivax relative to that in P. falciparum.

It is now recognized that the global morbidity from vivax malaria has been greatly underestimated, with Plasmodium vivax estimated to cause 130–435 million cases annually and 22%–40% of the global malaria burden [1]. Despite this, the pathophysiological aspects of P. vivax have been largely neglected.

Vivax malaria is a major cause of febrile illness in areas where it is endemic, and it is a significant contributor to anemia and low birth weight [2, 3]. However, except for placental dysfunction [3], organ-specific morbidity from P. vivax remains underrecognized and poorly studied. Whereas P. falciparum–infected red cells cytoadhere to the microvascular endothelium, causing mechanical microcirculatory obstruction and end-organ dysfunction, P. vivax is widely believed to be incapable of cytoadherence and microvascular sequestration and, therefore, is not thought to be a cause of organ dysfunction. Recent in vitro data suggested that P. vivax–infected red cells do cytoadhere to the endothelial cell ligand chondroitin sulfate A (CSA) [4], but this finding has not yet been substantiated in vivo. A recent study showed no evidence for P. vivax cytoadherence in the placenta [5]. However, autopsy and tissue biopsy studies of other organs in pure P. vivax infections...
have been very rare [6–9], and sequestration of *P. vivax*-infected red cells within organ microvasculature in vivo has not been fully excluded.

*P. vivax* has recently been shown to have caused acute respiratory distress syndrome (ARDS)/noncardiogenic pulmonary edema in at least 18 patients [10–23], a disease process previously thought to occur only in malaria caused by *P. falciparum* [24–26]. Abnormal pulmonary function has been observed in returned travelers with vivax malaria, including reduced alveolar gas transfer and increased pulmonary white cell activity [27]. However, the extent to which impaired gas transfer results from inflammation at the alveolar-capillary membrane (Dm) and/or sequestration of white cells or parasitized red cells within the alveolar microvasculature is not known. The partitioning of gas transfer measurement into its Dm and pulmonary capillary vascular (VC) components is a noninvasive tool that can be used to examine these questions. The reciprocal of the Dm component of gas transfer (1/Dm) measures the diffusion resistance extending from the alveolus (including any pathological alveolar fluid), the alveolar epithelium, the interstitium, and the capillary endothelium (including any adherent leukocytes) through to the plasma within alveolar capillaries [28, 29]. The reciprocal of the VC component of gas transfer (1/VCg) measures the oxygen-dependent transfer resistance per milliliter of blood (including the red cell membrane and intraerythrocytic hemoglobin) [28, 29]. We, therefore, studied patients with uncomplicated vivax and falciparum malaria, partitioning gas transfer into its Dm and VC components to characterize and compare the sites of impairment in gas transfer and to determine whether, in vivax malaria, there was evidence for vascular sequestration by white cells, parasitized red cells, or both.

With vivax malaria, the pyrogenic threshold (the level of parasitemia at which *P. vivax* causes fever) is known to be lower than that of falciparum malaria [30, 31]. Because of this, the inflammatory response to *P. vivax* has been hypothesized to be of greater magnitude than that to *P. falciparum*, with plasma levels of the fever-inducing cytokine tumor necrosis factor (TNF)–α being higher in vivax than in falciparum malaria in some studies [32, 33]. This hypothesis has not previously been tested at the level of organ function. Clinically apparent lung injury in falciparum malaria and particularly in vivax malaria most commonly develops after the start of antimalarial treatment [10–23, 25, 26] and is thought to be predominantly due to an inflammatory response [26, 27, 34, 35]. Therefore, in addition to performing assessments on presentation, we also compared the effects that each species has on Dm function after treatment.

### SUBJECTS AND METHODS

The present study was a prospective longitudinal observational comparative study of the physiological aspects of lung function in uncomplicated vivax and falciparum malaria. It was conducted between 2002 and 2004 at Mitra Masyarakat Hospital (RSMM) in Timika, Papua, Indonesia. In this lowland region of unstable malaria transmission, both *P. falciparum* and *P. vivax* are endemic: symptomatic malaria occurs at all ages, with an incidence of 620 cases/1000 person-years and a falciparum:vivax ratio of 55:45 [36].

Three groups of subjects ≥18 years old were enrolled from the outpatient clinic: (1) the vivax malaria group (*P. vivax* parasitemia, >400 parasites/μL; hemoglobin level, >8 g/dL; fever [axillary temperature ≥38°C] or history of fever within 48 h, with no other cause present; and no manifestations of severe malaria [34]); (2) the uncomplicated falciparum malaria group (criteria as above, with *P. falciparum* parasitemia, >1000 parasites/μL, previously described as part of a comparative study of lung injury in severe malaria [34]); and (3) healthy control subjects (defined elsewhere [34, 37]). Oral treatment was given as per prevailing RSMM and Indonesian Ministry of Health guidelines: 3 days of chloroquine and 14 days of primaquine (15 mg daily) for *P. vivax* and 7 days of quinine for *P. falciparum*. All research was conducted in accordance with national and institutional guidelines for human experimentation. The study was explained in the Indonesian language by local health providers and, where necessary, local language translators.

### Table 1. Proportion of subjects who attended follow-up as per protocol and who had adequate spirometric and gas transfer results suitable for analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 109)</th>
<th>Uncomplicated vivax malaria (n = 50)</th>
<th>Uncomplicated falciparum malaria (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reviews</td>
<td>...</td>
<td>94 (63)</td>
<td>93 (62)</td>
</tr>
<tr>
<td>Acceptable gas transfer</td>
<td>67 (61)</td>
<td>41 (44)</td>
<td>34 (37)</td>
</tr>
<tr>
<td>Acceptable spirometry</td>
<td>80 (73)</td>
<td>57 (61)</td>
<td>63 (68)</td>
</tr>
</tbody>
</table>

**NOTE.** Reviews data are total no. (% of total possible) of patients attending for review; acceptable gas transfer and spirometric data are no. (%) of patients or control subjects with adequate data out of those attending for review.
differences who agreed to participate were provided with a written information sheet in Indonesian and signed a consent form.

Subjects with malaria were assessed on the day of presentation to the clinic and again 7 and 14 days later, by use of a standardized assessment of clinical symptoms and signs, hemoglobin level, parasitemia, and lung function, as described elsewhere [34]. Cough was recorded as being present on the basis of patient history (either volunteered or elicited in response to direct questioning). Among control subjects, the 90th percentiles for respiratory rate and the median oxygen saturation were used to define cutoffs when comparing the frequency of tachypnea and reduced oxygen saturation, respectively, in each malaria group.

Measurements of gas transfer and lung volumes were undertaken as described elsewhere [34], by use of the single-breath technique (DLCOSB) corrected for hemoglobin [38, 39]. DLCO/SB was partitioned into its Dsl and Vc components (encompassing ΘCO and Vc volume, according to the Roughton-Forster relationship: \( 1/\text{DLCO} = 1/D_{sl} + 1/(\Theta CO \times V_c) \), where DLCO is mean pretreatment gas transfer) [28, 29]. To do this, DLCO SB was measured using a gas mixture of high and low oxygen concentration, with the high oxygen concentration mixture being preceded by 5 min of 100% oxygen breathing. Low oxygen measures of gas transfer were performed at least twice. Results of high and low oxygen gas transfer were only included for analysis if these duplicates agreed to within 10% and if breath-holding time was between 9 and 10 s. Spirometry was undertaken according to American Thoracic Society Guidelines [38], with quality assurance as described elsewhere [34].

Data were analyzed using Intercooled Stata (version 7.0; Stata) and SPSS (version 14; SPSS). Predicted values for gas transfer were derived for each ethnic group from the healthy control subjects and for spirometry from all control subjects by use of multivariate linear regression, as described elsewhere [34, 37]. Spirometry and gas transfer variables were expressed as the percentage of predicted values. Univariate statistics were used to compare calculated normal lung function values to those of subjects with malaria using Student’s t test for normally distributed data and the Wilcoxon rank sum test for nonparametric data. Univariate analysis of categoric variables used the chi-square test or Fisher’s exact test as appropriate. Linear regression was used to model changes over time, controlling for repeated measures, and with log transformation when necessary to achieve normal distribution of outcome measures.

RESULTS

Subjects included 50 patients with vivax malaria, 50 patients with uncomplicated falciparum malaria, and 109 healthy control subjects. The proportion of subjects who were assessed at baseline, who were available for review on follow-up, and who had adequate quality lung function tests are listed in table 1. Compared with control subjects, fewer patients with malaria had gas transfer results of adequate quality (\( P < .001 \)), but there was no difference between malaria species in the proportion having adequate results. Inability to perform or collect information from adequate quality lung function studies was not associated with sex, ethnic group, anemia, or previous antimalarial treatment.

Baseline demographics. Demographic and clinical details for those subjects who had cough data or at least 1 acceptable respiratory function test are shown in table 2. Cough data were obtained from 95% of patient reviews. Patients with malaria were more likely to come from the highlands than were control subjects (\( P = .001 \)). There was no significant difference in ethnic group, smoking history, or history of malaria between patients with vivax and those with falciparum malaria. Parasite density was significantly lower in patients with vivax malaria than in those with falciparum malaria (\( P < .0001 \)). Mean hemoglobin level at presentation was significantly lower in patients with vivax malaria than in those with falciparum malaria or in control subjects (\( P < .0001 \)). None of the patients with malaria died or developed ARDS. Of those with acceptable gas transfer results, only 1 patient had parasitemia during the follow-up period (an asymptomatic patient in the falciparum malaria group with low-level parasitemia [23 parasites/μL], on day 7 only).

Clinical evidence of respiratory involvement. There was no significant difference in cough rates for smokers or for other baseline characteristics. Patients with vivax malaria had a significantly higher frequency of cough (63% [31/49]) than control subjects (14% [15/105]) at presentation (odds ratio [OR], 10.3 [95% confidence interval [CI], 4.3–26.0]; \( P < .0001 \)) (figure 1). Cough frequency had returned to control levels by day 14. The proportion of patients with a baseline respiratory rate \( > 24 \) breaths/min was higher in patients with vivax malaria (33% [16/49]) than in control subjects (10% [10/105]) (OR, 4.6 [95% CI, 1.8–12.2]; \( P < .0001 \)) but was not significantly different from that in patients with falciparum malaria (47% [23/49]). At the time of presentation, the proportion of patients with vivax malaria with oxygen saturation \( < 98\% \) (22% [11/49]) was not significantly different from that of control subjects (15% [16/105]) but was significantly higher by day 7 (38% [9/24]; \( P = .02 \)). In contrast, the proportion of patients with falciparum malaria with oxygen saturation \( < 98\% \) was significantly higher than that of control subjects on presentation (39% [19/49]; \( P = .002 \)) but was no longer significant by day 7 (21% [5/24]). The mean decrease in oxygen saturation after 7 days was 0.61% (95% CI, 0.2%–1.0%; \( P < .01 \)) in patients with vivax malaria, compared with a mean increase of 0.64% (95% CI, 0.2%–1.0%; \( P = .03 \)) in those with uncomplicated falciparum malaria. No patients had oxygen saturation \( < 95\% \) at presentation.

Lung function tests. DLCO in patients with vivax malaria
Table 2. Demographic and clinical characteristics at presentation of subjects who had cough data or at least 1 acceptable respiratory function test.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (n = 109)</th>
<th>Uncomplicated vivax malaria (n = 50)</th>
<th>Uncomplicated falciparum malaria (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>27 (18–56)</td>
<td>24 (18–41)</td>
<td>23 (18–44)</td>
</tr>
<tr>
<td>Female</td>
<td>33 (36/109)</td>
<td>46 (23/50)</td>
<td>43 (21/49)</td>
</tr>
<tr>
<td>Papuan highlander</td>
<td>70 (75/107)</td>
<td>98 (49/50)</td>
<td>88 (43/49)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>38 (41/107)</td>
<td>28 (14/50)</td>
<td>33 (16/49)</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>157.8 (6.4)</td>
<td>155.5 (5.8)</td>
<td>156.6 (6.3)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>58.2 (8.1)</td>
<td>54.3 (6.4)</td>
<td>56.1 (8.1)</td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD), g/dL</td>
<td>12.6 (2.3)</td>
<td>10.0 (2.1)a</td>
<td>11.7 (2.2)</td>
</tr>
<tr>
<td>&lt;10 g/dL</td>
<td>13 (14/108)</td>
<td>55 (27/49)</td>
<td>19 (9/49)</td>
</tr>
<tr>
<td>White cell count, mean (SD), 10⁶ cells/L</td>
<td></td>
<td>6.6 (2.4)</td>
<td>5.9 (1.9)</td>
</tr>
<tr>
<td>Parasite density, geometric mean (range), parasites/µL</td>
<td>...</td>
<td>4290 (837–32,860)</td>
<td>14,294 (235–96,360)</td>
</tr>
<tr>
<td>Duration of fever before presentation, median (range), days</td>
<td>...</td>
<td>3 (1–21)</td>
<td>3 (0–14)</td>
</tr>
<tr>
<td>History of malaria</td>
<td>76 (80/105)</td>
<td>82 (41/50)</td>
<td>94 (46/49)</td>
</tr>
<tr>
<td>Treatment before presentation</td>
<td>30 (31/105)</td>
<td>40 (20/50)</td>
<td>31 (15/49)</td>
</tr>
</tbody>
</table>

**Note.** Data are percentage (no. with characteristic/total no. possible) of subjects with characteristic, unless otherwise indicated.

* Significantly fewer subjects in the vivax malaria group than in the falciparum malaria group (P < .001).

was 93% (95% CI, 87–104) of predicted values (P = .08). The mean percentage of predicted DLCO deteriorated progressively after treatment: by day 7, it had decreased to 88% (95% CI, 79–97; P = .01), and, by day 14, to 84% (95% CI, 72–95; P = .004) (figure 2). Linear regression confirmed progressive impairment in DLCO over the 2 weeks after treatment of vivax malaria (coefficient, −0.7% of predicted value/day; P = .02, r² = 0.10). In patients with falciparum malaria, DLCO was also significantly reduced after 7 days of treatment, with the impairment persisting until day 14 (figure 2).

Gas transfer was partitioned into its constituent Dm and Vc components. In patients with vivax malaria, the Vc volume was significantly reduced at presentation (mean, 72% of predicted value [95% CI, 57%–86%]; P = .009), to a level comparable to that seen in patients with falciparum malaria (figure 2). Vc volume improved on subsequent measurements in patients with both vivax and falciparum malaria and in both species was no longer significantly impaired by day 7 (figure 2).

There was no significant abnormality in Dm function in patients with vivax malaria at presentation, but there was a progressive deterioration in Dm function in the 2 weeks after treatment (linear regression coefficient, −1.0% of predicted value/day; P = .02, r² = 0.10 (figure 2). In contrast, although a similar trend was seen in uncomplicated falciparum malaria, linear regression showed no significant deterioration in Dm function over time.

In multivariate analysis, there was no significant relationship between parasitemia and gas transfer variables in patients with vivax malaria. There was no significant abnormality in spirometric results (forced vital capacity, forced expiratory volume in 1 s, or forced midexpiratory flow) in patients with vivax malaria.

**Discussion.**

Along with many other aspects of P. vivax infection, the pathophysiological aspects of vivax malaria have been largely neglected. The present study of the pulmonary physiological evidence demonstrates a reduction in the baseline Vc component of gas transfer in vivax malaria comparable to that found in
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Figure 2. Gas transfer (DLco) measures over time for patients with uncomplicated vivax and falciparum malaria. Data are mean percentages of predicted values and SE values. Black bars represent the control subjects, gray bars represent patients with uncomplicated vivax malaria, and white bars indicate patients with uncomplicated falciparum malaria. Comparison with controls: * P < .05; ** P < .01. Linear regression coefficient for the decrease in the alveolar-capillary membranous component of DLco (DM) in Plasmodium vivax: −1.0% of predicted value/day; P = .02, r² = .10. The decrease in DM function in P. falciparum was not statistically significant. DM, pulmonary capillary vascular component of DLco.

The reduction in VC volume indicates a reduction in the volume of hemoglobin-containing red cells within the pulmonary capillaries at the time of presentation. The most likely explanation is the encroachment on the hemoglobin-containing vascular compartment by sequestered leukocytes, parasitized red cells, or both. Although sequestration of leukocytes within the pulmonary microvasculature may well contribute to the subsequent impairment of DM function occurring in response to antimalarial treatment, it is unlikely to be the predominant cause of the impairment of baseline VC volume in either vivax or uncomplicated falciparum malaria because adherent leukocytes should also cause a parallel decrease in DM function, but this was not found with either Plasmodium species on presentation. In contrast, cytoadherence of red cells to the pulmonary vascular endothelium in which intraerythrocytic hemoglobin has been replaced by mature stages of P. vivax would be expected to reduce VC volume without a significant parallel decrease in DM function.

We, therefore, believe that sequestration of P. vivax–infected red cells may contribute to reduced pretreatment VC volume. In the absence of sequestration, peripheral parasitemia would be expected to be proportional to organ-specific dysfunction. The absence of any relationship between the level of P. vivax parasitemia and either gas transfer or VC volume supports the hypothesis that, as in the case of P. falciparum, mature stages of P. vivax–infected red cells sequester within the pulmonary microvasculature. Although all stages of P. vivax circulate in vivax malaria, their distribution is not uniform. Mature schizonts in blood films are nearly always less common than the trophozoites from which they arise [31]. Because of this, Field and Shute argued >50 years ago that in P. vivax infections “an appreciable proportion … complete their segmentation in the internal capillaries” [31]. Animal models of malaria also support a role for nonfalciparum Plasmodium species sequestering in the lung. Red cells parasitized with schizonts of P. vinckei and P. yoelii preferentially sequester within the pulmonary microvasculature [40]. Human autopsy studies in vivax malaria are rare, and the pulmonary findings are not definitive. Among 3 early 20th-century autopsy reports of vivax malaria cases (none of which showed lung injury before death or completely excluded coinfection with falciparum malaria), one described parasites in alveolar capillaries [9], one reported their absence in the pulmonary microvasculature (after quinine treatment) [7], and one did not comment on their presence or absence [8].

Although red cells infected with trophozoites of P. vivax do not appear to cytoadhere to the endothelial cell ligands, CD36 or intracellular adhesion molecule–1 [41], recent in vitro data have demonstrated cytoadherence of P. vivax–infected red cells to CSA [4], an endothelial cell ligand known to mediate sequestration of P. falciparum within the placental microvasculature. The other human endothelial cells known to

uncomplicated falciparum malaria and a significant and prolonged impairment of alveolar-capillary gas transfer developing after commencement of treatment. This reduction was more apparent than that occurring in uncomplicated falciparum malaria but was less apparent than that found in severe falciparum malaria [34]. These findings occurred despite a lower initial parasite burden in vivax malaria.
express CSA are those in the lung and brain [42, 43]. We speculate that cytoadherence of *P. vivax*–infected red cells to CSA or another ligand on the pulmonary endothelium may be a mechanism for any sequestration within the pulmonary microvasculature.

Other mechanisms of microvascular obstruction known to occur in falciparum malaria are unlikely to explain the reduction in $V_C$ volume. In contrast to the reduced red cell deformability in falciparum malaria, red cells in vivax malaria have increased deformability [44], which cannot explain reduced $V_C$ volume. Rosetting, the adherence of nonparasitized red cells to parasitized red cells, is known to occur in vivax malaria [41] and could contribute to reduced pulmonary blood flow. However, reduced flow and other potential causes of reduced $V_C$ volume such as vasoconstriction and pulmonary hypertension have not previously been found to cause reduced $V_C$ volume without also causing reduced $D_M$ function [29, 45, 46]. Pulmonary congestion from heart failure causes normal or increased $V_C$ volume and reduced $D_M$ function [47]. The pattern of uncoupling that we report in vivax and falciparum malaria [34] has not, to our knowledge, otherwise been described.

The progressive impairment of $D_M$ function was statistically significant after treatment of vivax malaria but not after treatment of uncomplicated falciparum malaria. The reduction in $D_M$ function represents alveolar-capillary dysfunction, with potential causes including endothelial injury, alterations in endothelial permeability causing interstitial and alveolar edema, and intravascular sequestration of leukocytes. An inflammatory cause is supported by autopsy studies in vivax malaria showing increased alveolar-capillary monocytes [8] and isotopic studies showing increased pulmonary phagocytic cell activity 1–2 days after the commencement of treatment for vivax malaria [27]. This likely reflects a posttreatment intravascular inflammatory response to the death of parasites or reperfusion and is consistent with the fact that all clinical cases of ARDS in vivax malaria that have included a treatment history [10–23] have occurred after the start of treatment. If vivax parasites do preferentially sequester in the lung, this may target the posttreatment inflammatory response to the lungs rather than to other organs, with both phenomena potentially explaining why vivax malaria causes lung injury.

Our finding of significant progressive alveolar-capillary dys-function after treatment of vivax malaria but not uncomplicated falciparum malaria, despite a lower initial parasitemia, is consistent with a greater inflammatory response to a given parasite burden in *P. vivax*, compared with that in *P. falciparum*. This is also supported by the subclinical changes in oxygen saturation, which improved after treatment in uncomplicated falciparum malaria but decreased after treatment in those with vivax malaria. These organ-specific findings are consistent with previous studies comparing the systemic inflammatory response between species, with higher plasma levels of the fever-inducing cytokine TNF-α in vivax than in falciparum malaria in some [32, 33] but not all studies.

As in our previous studies of severe malaria [34], confounding factors are unlikely to explain the gas transfer findings. Fever alone is an unlikely factor, because gas transfer worsened after the subjects became afebrile, and overall diffusing capacity is not greatly influenced by temperature [29]. Differential effects of fever on $D_M$ function and $V_C$ volume are reported to be negligible [29]. Anemia, which is worse in patients with vivax malaria, is taken into account with a correction factor applied in the derivation of $D_{LCO}$ [28, 29]. Spirometric results were normal in vivax malaria and cannot explain the reduction in gas transfer. There remains some uncertainty relating to the assumption implied in the derivation of $\theta$, the reaction rate for CO with red cells. Although we cannot exclude an alteration in $\theta$ due to changes in internal red cell viscosity, membrane physicochemical properties, red cell shape, and alterations in hemoglobin in vivax malaria, $\theta$ does not appear to be significantly altered in red cells infected with *P. falciparum* when controlled for hemoglobin concentration (B. Russell, Menzies School of Public Health Research, Darwin, personal communication). There was no difference in the proportion of patients with vivax and falciparum malaria with gas transfer studies of adequate quality, and this is unlikely to account for the differences in gas transfer between the groups.

Chloroquine has anti-inflammatory effects. These may have attenuated inflammatory changes after treatment of vivax malaria, and our estimates of reduced $D_M$ function may be conservative. Because chloroquine-resistant vivax malaria spreads [2], it is possible that use of drugs without anti-inflammatory effects may lead to an increase in the incidence of acute lung injury in vivax malaria. Supervised high doses of primaquine can result in modest but clinically insignificant levels of methemoglobinemia. The lower primaquine dose administered in the present study and the known poor compliance with prolonged courses make it unlikely that primaquine-induced methemoglobinemia would have significantly confounded gas transfer findings. Methemoglobinemia should not affect $D_M$ function, although it may possibly reduce $V_C$ volume. However, $V_C$ volume was impaired before primaquine administration and had normalized by day 7, by which time any drug-induced methemoglobin would have had its effect.

As was previously found in nonimmune travelers [27], cough also occurred in the majority of adults with vivax malaria living in a malaria-endemic area. Vivax malaria is likely to be underrecognized as a cause of fever and cough in areas of endemicity and, as with *P. falciparum* infection [48], may be mistaken for acute respiratory infection [27]. Studies in Indonesian children have shown that cough and chest crackles are at least as common in vivax as in falciparum malaria [49]. The respi-
ratory manifestations of vivax malaria may have implications for the syndromic treatment of fever, cough, and fast breathing in young children. In areas where *P. falciparum* is endemic, the World Health Organization has recommended treatment for both malaria and pneumonia [50]. Prospective studies are necessary to determine the magnitude of overlap in clinical presentations between vivax malaria and pneumonia and whether these recommendations need to be extended to vivax malaria–endemic areas.

In conclusion, the membranous and vascular components of gas transfer are uncoupled in vivax malaria, both at presentation and after treatment. The reduction in $V_C$ volume on presentation without impairment of $D_M$ function suggests that, before treatment, the reduced $V_C$ volume of hemoglobin-containing cells may be due to the sequestration of parasitized red cells more than leukocytes within the pulmonary vasculature. The return of $V_C$ volume to normal after treatment is consistent with the clearance of sequestrated parasitized cells. The progressive and significant decrease in $D_M$ function after treatment suggests prolonged alveolar-capillary injury, which we hypothesize is due to an inflammatory response to parasite killing or reperfusion. If vivax parasites do preferentially sequester in the lung, this may target this posttreatment inflammatory response to the lungs rather than other organs, with both phenomena potentially explaining why vivax malaria causes lung injury but rarely injury to other organs. The posttreatment decrease in $D_M$ function with treatment was statistically significant in vivax malaria but not in uncomplicated falciparum malaria and occurred despite a lower mean parasitemia. This is consistent with the inflammatory response to the toxins of *P. vivax* being greater than that to the toxins of *P. falciparum*.

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