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Cardiovascular changes in patients with non-severe Plasmodium vivax malaria

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Abstract

Background: Cardiovascular system involvement in patients with Plasmodium vivax malaria has been poorly addressed. The aim of this study was to evaluate cardiac structures and function, and serum markers of cardiovascular injury in patients with the non-severe form of vivax malaria in Manaus, Amazonas State, Brazil.

Methods and results: We prospectively evaluated 26 patients with vivax malaria in an outpatient referral hospital and compared results with a control group of 25 gender- and age-matched healthy individuals. Patients underwent clinical evaluation, laboratory tests, and transthoracic echocardiography at first evaluation (day zero, D0) and seven days (D7) after malaria diagnosis. At D0 echocardiography showed higher left ventricular (LV) systolic diameter (28.8 ± 2.82 vs 30.9 ± 4.03 mm; p = 0.037) and LV diastolic volume (82.4 ± 12.3 vs 93.8 ± 25.9 ml; p = 0.05), and lower LV ejection fraction (Teicholz method: 73.2 ± 6.59 vs 68.4 ± 4.87%; p = 0.004) in patients compared to controls. Right ventricle (RV) fractional area change (54.7 ± 5.11 vs 50.5 ± 6.71%; p = 0.014) was lower, and RV myocardial performance index (0.21 ± 0.07 vs 0.33 ± 0.19; p = 0.007), and pulmonary vascular resistance (1.13 ± 0.25 vs 1.32 ± 0.26 Woods unit; p = 0.012) were higher in patients than controls. Patients presented higher serum levels of unconjugated bilirubin (0.24 ± 0.15 vs 1.30 ± 0.89 mg/dL; p < 0.001), soluble vascular cell adhesion molecule–1 (sVCAM-1; 453 ± 143 vs 1983 ± 880 ng/mL; p < 0.001), N-terminal prohormone brain natriuretic peptide (0.59 ± 0.86 vs 1.83 ± 0.57 pg/mL; p < 0.001), and troponin T (861 ± 338 vs 1037 ± 264 pg/mL; p = 0.045), and lower levels of plasma nitrite (13.42 ± 8.15 vs 8.98 ± 3.97 μM; p = 0.016) than controls. Most alterations had reversed by D7.

Conclusion: Patients with non-severe Plasmodium vivax malaria present subclinical reversible cardiovascular changes.

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1. Introduction

Malaria, a common parasitic disease affecting humans, is one of the most important public health issues in developing countries [1]. In 2013, there were 104 countries with endemic malaria, with approximately 198 million people affected and an estimated 584 thousand deaths [1].

Malaria pathophysiology has been extensively studied. However, since the first reports by Laveran [2] in 1884 describing myocardial and coronary changes in patients dying from malaria, few studies have carefully evaluated the cardiovascular system in malaria. These clinical and experimental studies have suggested that acute infection is accompanied by parasite sequestration and obstruction in microvascular coronary and myocardial injury caused by parasite released proteins as well as inflammatory cytokines and anemia [3–8]. More recently, falciparum malaria patients were shown to present endothelial
dysfunction with impaired vascular nitric oxide bioavailability and increased pulmonary artery pressure [4,9]. All studies on cardiovascular involvement in malaria have been performed on Plasmodium falciparum malaria, which is related to the most severe form of the disease affecting several organs and systems [10]. Of the various Plasmodium species, Plasmodium vivax was previously considered to cause a benign non-fatal infection. However, in the last decade several reports have linked P. vivax to systemic complications involving the central nervous system, renal and respiratory failure, abnormal bleeding, anemia, and jaundice [11–16]. To the best of our knowledge, there are no studies analyzing the cardiovascular system during P. vivax malaria. In this study, we evaluated cardiac structures and function by Doppler-echocardiogram and plasmatic markers of cardiovascular injury in patients with the non-severe form of P. vivax malaria in Manaus, Amazonas State, Brazil.

2. Materials and methods

2.1. Study subjects

In a case–control study, we prospectively evaluated outpatients with P. vivax malaria attending the Dr. Heitor Vieira Dourado Tropical Medicine Foundation (FMT–HVD), in Manaus, Brazil, between December 2012 and March 2013. The FMT–HVD is a tertiary care center for infectious diseases, where patients can either seek attention directly or be referred for specialized care in neighboring municipalities. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by FMT–HVD Research Ethics Committee. All individuals signed the informed consent.

Patients aged 18–60 years were eligible to participate if they had no known illness and were diagnosed with P. vivax malaria to be treated out of hospital (P. vivax group, n = 26). Age and gender-matched individuals testing negative for malaria comprised the Control group (n = 25). The controls had similar economic conditions and lived in the same neighborhood as the patients. Exclusion criteria included electrocardiographic changes suggesting regional abnormalities, heart valve disease, and previously diagnosed severe diseases such as stage C heart failure, renal or liver insufficiency, cancer, pregnancy, malaria other than P. vivax, or severe malaria needing in-hospital treatment according to the World Health Organization [1]. All patients had positive thick blood smear and real-time qPCR assay for P. vivax malaria. Controls tested negative in both tests. Patients were treated with a combination of chloroquine and primaquine or a combination of artesunate and amodiaquine.

All individuals were subjected to the following: medical history evaluation, physical examination, 12-lead resting electrocardiogram, thoracic Doppler-echocardiogram, and laboratory investigation. In patients, clinical and laboratory evaluation was performed before treatment (day zero, D0) and seven days after starting treatment (day seven, D7). Medical history and physical examination were performed to assess general health and to clinically exclude diseases or conditions described in the exclusion criteria. Blood pressure was measured by the auscultatory technique with a conventional mercury sphygmomanometer.

2.2. Echocardiographic evaluation

A standard echocardiography system (General Electric Medical Systems, Vivid 3) was used to measure cardiac structures as previously described and following American Society of Echocardiography recommendations [17–20]. All echocardiograms were performed by the same examiner (JMBBF). With individuals positioned in left lateral decubitus position and monitored with an electrocardiographic lead, the following echocardiographic cuts were performed: short parasternal axis to measure ventricles, aorta and left atrium; apical 2, 4 and 5 chambers to evaluate ventricular cavities and systolic and diastolic function. The average of three measurements was calculated for each variable. The following left ventricular (LV) structures were measured by two-dimensional guided M-mode images: diastolic and systolic diameters (LVDD and LVSD, respectively), and diastolic and systolic volume (LVDV and LSVV, respectively). LV systolic function was evaluated by measuring ejection fraction according to the Teicholz index, endocardial fractional shortening, and myocardial performance index (Tei index) [21]. Right ventricle (RV) was structurally evaluated by measuring diastolic and systolic areas. RV systolic function was evaluated by fractional area change (FAC), and Tei index. Pulmonary vascular resistance (PVR) was estimated by Doppler echocardiography [22] according to the formula: PVR = tricuspid regurgitation peak velocity/right ventricular outflow tract velocity time integral) X 10 + 0.16. Pulmonary artery systolic pressure (PASP) was estimated by Doppler echocardiography using the modified Bernoulli equation 22: PASP = 4 X (tricuspid regurgitation peak velocity) [2] + right atrial pressure. Right atrial pressure was estimated from inferior vena cava diameter [22].

2.3. Laboratorial analysis

Venous blood samples were obtained after a 12–15 h overnight fast in EDTA-coated tubes. Plasma was frozen at −80 °C in tubes containing 5 μL/mL antioxidant butyl hydroxytoluene (BHT, 20 μM), proteases inhibitor (aprotinin, 2 mg/mL), phenylmethylsulphonyl fluoride (PMSF, 1 mM), and benzamidine (2 mM). Nitrite plasma concentration was quantified by colorimetry using a commercially available nitric oxide assay kit (Cayman, Chemical Company, Ann Arbor, Michigan, USA). Concentrations of N-terminal prohormone brain natriuretic peptide (NT-proBNP) and troponin T were measured by ELISA using commercially available kits (USCN Life Science Inc., Houston, Texas, USA). Soluble vascular cell adhesion molecule (sVCAM)-1 concentration was analyzed by immunoassay using a commercially kit (R&D Systems, Inc., Minneapolis, Minnesota, USA). All kits used in this study are available for laboratory research use only, but not for human diagnostics.

Subjects were tested for malaria by thick blood smear. Parasite density was calculated from the arithmetic mean of two concordant readings; the white blood cell count was obtained from total blood count analysis as previously described [23]. In case of discordance (species-specific, or in the density quantification whenever a discrepancy was higher than 10%), a third reading was performed by a senior investigator (WMM). Real-time qPCR was performed as previously described [24] to confirm P. vivax malaria.

2.4. Statistical analysis

Variables are presented as mean and standard deviation or median and minimum and maximum values. Comparisons between periods were performed by Student’s t test for dependent data and comparisons between groups were performed by unpaired Student’s t test. Categorical parameters were compared by Fisher’s exact test. The association between variables was assessed with Pearson’s correlation coefficient. The level of significance was 5%. Statistical analyses were performed using IBM SPSS Statistics software Version 21.

3. Results

Baseline characteristics for controls and patients at day zero (D0) are presented in Table 1. Heart rate, although within the normal range, was higher in P. vivax group than Controls. The P. vivax group had a mean peripheral parasitemia of 2844 ± 3286 parasites/mm³, ranging from 87 to 11,806 parasites/mm³. Laboratory data are shown in Table 2. P. vivax D0 had increased plasma concentrations of unconjugated bilirubin, troponin T, NT-proBNP, and sVCAM-1 and decreased platelet count and nitrite levels compared to Controls. At D7, unconjugated bilirubin, troponin T, NT-proBNP, and sVCAM-1 were lower, and platelet count and nitrite levels higher than D0. Sixty
Nitric oxide depletion also impairs vasodilation [33]. In this study, plasma concentration of sVCAM-1 was higher and nitrite levels lower than Controls suggesting a low degree of hemolysis. Malaria patients had a slight decrease in platelet count at D0, which is compatible with falciparum malaria [4] and endothelial activation was previously observed in uncomplicated vivax malaria [34]. Nitrite is considered as a physiological storage pool of nitric oxide that can be reduced to bioactive nitric oxide in hypoxic conditions to mediate physiological responses in blood and tissue [35]. D7 sVCAM-1 was lower and nitrite higher than at D0 in malaria patients.

4. Discussion

In this study we evaluated cardiac structures and function by Doppler echocardiography and systemic markers of cardiovascular injury in patients with the non-severe form of P. vivax malaria at the beginning of infection and seven days later.

Malaria was diagnosed by examining thick blood smears and P. vivax malaria was confirmed by real-time qPCR assay. As jaundice is a diagnostic criteria for severe malaria, no icteric patient was included in this study. Nonetheless, mean unconjugated bilirubin values were higher at D0 in P. vivax than Controls suggesting a low degree of hemolysis. Malaria patients had a slight decrease in platelet count at D0, which is commonly observed in vivax malaria and may be related to platelet phagocytosis [25,26]. Platelet counting often normalizes after treatment [25].

As markers of myocardial injury, we evaluated plasma concentrations of troponin T and NT-proBNP, which were higher at D0 in P. vivax than Controls and D7 P. vivax. The troponin T levels in our patients were lower and with Tei index (r = 0.493; P = 0.01) and pulmonary vascular resistance, and lower fractional area change than Controls. In P. vivax patients, fractional area change was higher and pulmonary vascular resistance lower in D7 than D0. At D0, NT-proBNP levels positively correlated with RV diastolic (r = 0.409; P = 0.038) and systolic (r = 0.435; P = 0.026) areas and with Tei index (r = 0.493; P = 0.01) and pulmonary vascular resistance positively correlated with RV Tei index (r = 0.646; P < 0.001) in malaria patients.

Baseline characteristics at day zero (D0).

<table>
<thead>
<tr>
<th>Control (n = 25)</th>
<th>P. vivax (n = 26)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>44.5 ± 8.43</td>
<td>41.7 ± 13.7</td>
</tr>
<tr>
<td>Female, %</td>
<td>44.0</td>
<td>30.8</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.67 ± 0.07</td>
<td>1.67 ± 0.08</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>79.3 ± 15.0</td>
<td>79.0 ± 13.9</td>
</tr>
<tr>
<td>BMI</td>
<td>28.3 ± 4.54</td>
<td>28.2 ± 5.07</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>121 ± 11.6</td>
<td>121 ± 12.2</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>79 ± 8.6</td>
<td>78 ± 8.1</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66 ± 7.6</td>
<td>76 ± 13.2</td>
</tr>
</tbody>
</table>

Data are mean and standard deviation. BMI: body-mass index (weight in kilograms divided by the square of height in meters); and bpm: beats/min. Unpaired Student’s t test or Fisher’s exact test (*).

Table 2

Laboratorial data.

<table>
<thead>
<tr>
<th>Control (n = 25)</th>
<th>P. vivax D0 (n = 26)</th>
<th>P. vivax D7 (n = 26)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCBL, mg/dL</td>
<td>0.24 ± 0.15</td>
<td>1.22 ± 0.89</td>
<td>0.33 ± 0.15</td>
</tr>
<tr>
<td>Platelets, X 1000 cells/mm³</td>
<td>281 ± 64</td>
<td>145 ± 60</td>
<td>341 ± 77</td>
</tr>
<tr>
<td>Troponin T, pg/mL</td>
<td>861 ± 338</td>
<td>1037 ± 264</td>
<td>784 ± 249</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>0.59 ± 0.86</td>
<td>1.08 ± 0.81</td>
<td>0.63 ± 0.51</td>
</tr>
<tr>
<td>sVCAM-1, ng/mL</td>
<td>453 ± 143</td>
<td>1983 ± 880</td>
<td>849 ± 467</td>
</tr>
<tr>
<td>Nitrite, μM</td>
<td>13.4 ± 8.15</td>
<td>8.98 ± 3.97</td>
<td>12.3 ± 5.30</td>
</tr>
</tbody>
</table>

Data are mean and standard deviation. D0: day zero; D7: day seven; UCBL: unconjugated bilirubin; NT-proBNP: N-terminal prohormone brain natriuretic peptide; sVCAM-1: soluble vascular cell adhesion molecule; unpaired Student's t test P. vivax D0 vs Control; and paired Student's t test P. vivax D7 vs P. vivax D0.

The troponin T levels in our patients were higher than Controls and D7 in the P. vivax group. Right ventricular dilation may be the first indicator of an acute increase in pulmonary vascular resistance; and increased pulmonary vascular resistance can be related to vasoconstriction, inflammation, and obstruction of pulmonary arteries in malaria [22,37].

Further studies evaluating the markers of myocardial injury and vasodilation in the chronic phase of P. vivax malaria are needed.
Infectious myocardial injury during infection, depleted nitric oxide-induced increase in afterload, and/or nitric oxide depletion decreases vasodilation therefore increasing pulmonary bioavailability. Increased expression of cellular adhesion molecules on infected red blood cells induce a reduction in plasma nitrite, which is related with *P. vivax* malaria. Products from low grade hemolysis of parasitized red cells are needed to evaluate a larger sample of both *P. falciparum* and *P. vivax* malaria, which allowed us to raise a hypothesis on the pathophysiology of severe malaria.

<table>
<thead>
<tr>
<th>Control</th>
<th>D0</th>
<th>D7</th>
<th>D0 vs Control</th>
<th>D7 vs D0</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA, cm²</td>
<td>13.0 ± 3.19</td>
<td>15.3 ± 2.96</td>
<td>15.1 ± 2.55</td>
<td>0.009</td>
</tr>
<tr>
<td>SA, cm²</td>
<td>6.41 ± 1.27</td>
<td>7.45 ± 1.46</td>
<td>6.90 ± 1.41</td>
<td>0.009</td>
</tr>
<tr>
<td>FAC, %</td>
<td>54.7 ± 5.11</td>
<td>50.5 ± 6.71</td>
<td>55.7 ± 6.90</td>
<td>0.014</td>
</tr>
<tr>
<td>Tei index</td>
<td>0.21 ± 0.07</td>
<td>0.33 ± 0.19</td>
<td>0.27 ± 0.10</td>
<td>0.007</td>
</tr>
<tr>
<td>PVR, Wood units</td>
<td>1.13 ± 0.25</td>
<td>1.32 ± 0.26</td>
<td>1.17 ± 0.19</td>
<td>0.012</td>
</tr>
<tr>
<td>PASP, mm Hg</td>
<td>19.2 ± 2.95</td>
<td>19.7 ± 3.05</td>
<td>19.8 ± 4.19</td>
<td>0.057</td>
</tr>
</tbody>
</table>

Data are mean and standard deviation. D0: day zero; D7: day seven; DA: diastolic area; SA: systolic area; FAC: fractional area change; PVR: pulmonary vascular resistance; PASP: pulmonary arterial systolic pressure. Unpaired Student’s t test P. vivax D0 vs Control; and paired Student’s t test P. vivax D7 vs P. vivax D0.

We have not identified any other studies in literature evaluating cardiac structures and function in patients with vivax malaria. Our data suggest that outpatients with *P. vivax* malaria present subclinical cardiovascular changes and allow us to hypothesize that events previously described in severe *falciparum* malaria [4,9,38,39] also occur in non-severe vivax malaria. Products from low grade hemolysis of parasitized red blood cells induce a reduction in plasma nitrite, which is related with nitric oxide bioavailability. Increased expression of cellular adhesion molecules such as sVCAM-1 facilitates adherence to vascular endothelium and destruction of infected reticuloocytes and non-infected erythrocytes. Nitric oxide depletion decreases vasodilation therefore increasing pulmonary vascular resistance and impairing right ventricular function. Additionally, left ventricular dilation and dysfunction may result from infection, depleted nitric oxide-induced increase in afterload, and/or microscopic obstruction. The increase in NT-proBNP, suggesting dilation of cardiac chambers, and troponin T, suggesting myocardial injury, re-inforces myocardial injury during *P. vivax* malaria. Most alterations are reversible seven days after treatment.

### 5. Limitations

This study evaluated a small sized sample of outpatients with vivax malaria, which allowed us to raise a hypothesis on the pathophysiological events involved in cardiovascular changes. Therefore, additional studies are needed to evaluate a larger sample of both *P. vivax* malaria in- and out-patients in order to confirm our results and to extend the understanding of *vivax* malaria to patients with the severe form of the disease.

In conclusion, patients with non-severe *P. vivax* malaria present subclinical cardiovascular changes.

### Conflicts of interest

The authors report no conflicts of interest.

### Acknowledgements

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### References

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