The use of ECMO in treating a patient with shock due to Plasmodium falciparum malaria and myocarditis

Ng Kwan Chung Kenneth1*, Lim Yeong Pang1 and Leong Hoe Nam2
1Cardiologist, Novena Heart Centre, 38 Irrawaddy Road, #06-42, Singapore 329563, Republic of Singapore, 2Medical director, Rophi Clinic, 38 Irrawaddy Road, #07-55, Singapore 329563, Republic of Singapore.

Introduction
Myocardial involvement is an uncommon presentation in falciparum malaria [1]. There had been previous case reports of myocarditis due to Plasmodium falciparum and P. vivax malaria [2,3]. Of the nine reported cases, there were six deaths, making a mortality rate of 67%. This compares poorly to the expected long term survival (≥90%) of patients with viral myocarditis [4]. We describe the first successful treatment of a patient with severe Plasmodium falciparum malaria complicated with myocarditis and cardiogenic shock. He was treated with ECMO (extra corporeal membrane oxygenation) and survived despite having had multi-organ failure.

Case presentation
A 61 year old man was admitted to the hospital on 28 December 2013 at 10:58 with complaints of cough, fever, vomiting and poor appetite for three days. He had no significant past medical history. He had returned from a trip to a remote part of Indonesia two weeks prior to the illness. He worked in the jungles and had not taken any chemoprophylaxis against malaria.

On presentation at the emergency department, he had a fever of 39.5 degrees Celsius, respiratory rate of 20/min, heart rate of 122 beats per minute and the oxygen saturation was 95%. Bedside glucose test showed “HHH” indicative of a very high reading. Subsequently serum glucose was shown to be 630mg/dL. At presentation, he was lucid and orientated to time, person and space. The provisional diagnosis was pneumonia and newly diagnosed poorly controlled diabetes mellitus. The initial blood tests showed a normal total white cell count, low platelet count of 113,000, sodium of 129 mmol/L and bicarbonate of 17 mmol/L. The ECG done showed only Q waves in the anteroseptal leads. Blood gas did not demonstrate acidosis.

At 14:00, he became restless, confused, and hypoxic. He received supplemental 35% oxygen
and was transferred to the intensive care unit. He was diagnosed and managed as for hyperosmolar hyperglycemic non-ketotic state and was on intravenous regular insulin at 2 units/hour. At 17:05, malaria parasite was demonstrated in his blood on blood film. The patient was given intravenous artesunate and oral doxycycline and broad spectrum antibiotic cover [5].

At 18:00, the heart rate had risen to 154 bpm and the blood pressure was stable at 132/91 mmHg. He became tachypneic (respiratory rate 35 bpm) and confused. His peripheries were hypoperfused. An arterial blood gas showed a pH of 7.4, PO$_2$ of 106 mmHg, PCO$_2$ of 23 mmHg and oxygen saturation of 98%.

The CRP was 123 mg/L, procalcitonin 8.5 μg/L, HBA1c 11.6%, high sensitive troponin T of 1050 ng/L, mild transaminitis, blood bilirubin was 45 umol/L, blood ketone was 0.8 mmol/L, NT-pro BNP was 1640 pg/ml and lactate 3.15 mmol/L. Blood film demonstrated *P. falciparum* 10/1000 RBC on the blood film. Serological and other blood tests were negative for dengue, influenza, leptospirosis, and legionella. Bedside echocardiogram showed a left ventricular ejection fraction (LVEF) of 35% and regional wall motion abnormalities. An intraaortic balloon pump (IABP) and a central venous line were inserted. The IABP was set at 1:2 and the BP was maintained at 105/93 mmHg.

The patient remained confused and restless and the BP fell to systolic 60 mmHg. Intravenous colloids were given and intravenous adrenaline was started at 0.01 mcg/kg/min and titrated upwards to maintain mean pressure above 80 mmHg. Airway was secured with intubation. The BP drifted further to 78/44 mmHg and he remained tachycardic at 121 bpm. At 00:30 on 29 December 2013, despite best efforts of fluid resuscitation and inotropic support, the BP remained low. A repeat bedside echocardiogram showed that the left ventricle was hardly contracting with LVEF of about 10%. A decision was made for extracorporeal oxygenation. Venoarterial ECMO using a MAQUET PLS (Rastatt, Germany) with a quadrox oxygenator and rotaflow pumphead was inserted at bedside. The left common femoral artery was cannulated using a 15 French HLS arterial cannula (Bioline coated) and the right common femoral vein was cannulated using a 19 French HLS cannula (Bioline coated). The BP at 02:00 was 105/43 mmHg and heart rate was 115 bpm. Concurrently, his sugar control improved with intravenous regular insulin. Bedside glucose test fell to 288 mg/dL at 17:00 to 153 mg/dL at 02:00 the next day. He was then transferred to another hospital with more experience in the management of patients on ECMO. He arrived at the hospital on intravenous adrenaline 0.7 mcg/kg/min and noradrenaline 0.05 mcg/kg/min, ECMO and IABP at 1:1. The blood pressure was maintained at 108/54 mmHg but biochemically, the creatinine had climbed to 220 umol/L. The repeat labwork showed a CRP of 176 mg/L and procalcitonin of 174.5 μg/L. In the preceding eight hours, he passed out 720mls of urine. However, the next day, the urine output fell drastically and he was started on dialysis and the inotropes were maintained on intravenous noradrenaline at 0.6 mcg/kg/min. The managing team decided that the hypotension was more related to sepsis. Expectedly, he developed thrombocytopenia and platelet infusions were provided daily. The activated clotting time was maintained between 160 to 180 seconds. The ECMO was kept for four days. Throughout ECMO use, his conscious status improved and he became lucid. Serial echocardiograms done showed a gradual improvement in the LVEF from 10% to 20% and subsequently 38% on 2 January 2014. The ECMO was explanted on day 4 of support and he continued to improve clinically with a return of the urine production. The IABP was taken off one day later after he was cardioverted from an episode of atrial fibrillation. His BP continued to stabilise and he was weaned off inotropes. He was extubated another two days later and dialysis was stopped as his urinary output returned to normal. The malaria parasite on the blood film became negative on 8 January 2014. Less than a week later, he had full recovery of his renal and liver function. He remained lucid and ambulated well in the hospital ward. Refer to (Table 1) for serial changes in the blood chemistry throughout his stay in the intensive care unit.

In view of the regional wall motion abnormalities detected on transthoracic echocardiogram and the depressed LVEF of 38%, we performed a coronary angiogram on 13 January 2014. The coronary angiogram showed a 100% occluded right coronary artery proximally and a 60% stenosis of the proximal left anterior descending coronary artery, totally occluded first diagonal branch and a 100% occlusion of a large obtuse marginal branch. He underwent a coronary artery bypass surgery on the 20 January 2014. He recovered well with no complications and was discharged six days later, or 28 days after the initial presentation. The repeat transthoracic just before his discharge showed an improvement of LVEF to 55%.

**Discussion**

The unfortunate gentleman presented with severe *P. falciparum* malaria by the WHO criteria with altered mental state, jaundice, metabolic acidosis, hyperlactataemia and progressive renal impairment [5]. This was further complicated with hypotension. This complication occurred in up to 21% of patients in *P. falciparum* malaria presenting to an intensive care unit in Orissa, India [6]. It is difficult to ascertain the exact cause of the shock as malaria can cause septic shock and this can further lead to a decreased left ventricular systolic function (s=33%) and an increase in the left ventricular end-diastolic diameter [7]. In our patient, we felt that fulminant myocarditis was most likely the cause of the severe myocardial dysfunction as evidenced by a very low LVEF and the significantly elevated levels of high sensitivity troponin T and NT-pro BNP. However, we did not do a myocardial biopsy to document lymphocytic infiltration of the myocardium and an alternative explanation of the depressed myocardial function could be global subendocardial ischemia due to significant coronary artery disease and severe hypotension. The expected mortality was high and the family had been warned of the poor prognosis. Indeed it could be rapidly fatal as was reported in a case report of a German couple who succumbed to *Plasmodium* malaria induced myocarditis.
within five hours of the start of symptoms [8]. There had been scattered reports of myocardial involvement in the published literature and in one centre in India, the mortality rate was 50% [9]. Previous reports on survivors who had falciparum malaria and myocarditis developed respiratory distress from pulmonary edema diagnosed clinically or on a chest X-ray. In both cases, transthoracic echocardiogram showed a depressed LVEF [9,10]. One patient recovered with diuretics and digoxin and the other needed dobutamine and milrinone to improve the cardiac contractility but in both cases there was no reported hemodynamic instability. In another case report of myocarditis in a Korean lady with P. vivax malaria, the diagnosis was made on the complaint of chest pain, ECG changes and a mild rise in CKMB and troponin I, but the transthoracic echocardiogram showed a normal LVEF [11]. The MRI showed an abnormally high intensity signal in the myocardium. Her symptoms were mild and she did not suffer any adverse events. Our patient conversely had a more severe presentation with a very high respiratory rate, sinus tachycardia and hemodynamic compromise and a severely depressed LVEF. His presentation is more consistent with the description of fulminant myocarditis which is defined as severe hemodynamic compromise requiring high doses of vasopressors and at least two of the following: fever, distinct onset of symptoms and a recent viral illness within the last two weeks [4]. The pathogenesis of fulminant myocarditis due to a viral illness is similar to a proposed mechanism of toxic effects on the myocardium mediated by monokines such as tumour necrosis factor triggered off by the malarial parasites [11,12]. Our patient's presentation is quite similar to the second case reported in Dr. Kumar's paper in which a 15 year old patient died...
after developing hypotension and being on multiple inotropes. The presence of previously undiagnosed severe coronary artery disease may have further impaired his cardiac response to the sepsis and contributed to the hemodynamic instability. The use of ECMO in septic adult patients is certainly controversial [13]. Dr. MacLaren described that early deaths could be caused by refractory hypotension, progressive ventricular dilatation and cardiogenic shock. In this case, the patient became hemodynamically unstable and there was evidence of severe myocardial dysfunction in spite of inotropic support and support with an intraaortic balloon pump. Early intervention with ECMO helped to stabilise the blood pressure and maintain perfusion to the vital organs in order to prevent multiorgan failure and allow the heart to rest so that the myocardial function could improve subsequently. This is corroborated by Chen and colleagues who reported the use of ECMO in 15 patients with fulminant myocarditis and had a 93.3% weaning rate and a 73.3% discharge survival rate [14]. Their mean duration of ECMO support was 5.3 days which is about 1 day longer than the duration of ECMO in our patient. MacCarthy et al., also reported a good long term survival rate of 93% amongst patients with fulminant myocarditis and who were treated aggressively with inotropic support and or mechanical device [4].

In our patient, we felt that the use of ECMO with aggressive medical management and support of various organ function helped turned the tide against him. He remained in the intensive care unit for about seven days and had fully recovered and was able to ambulate by the end of the second week stay in hospital. This aggressive intervention may have shortened his stay in the intensive care. This compares very favourably to a similar patient in Germany who had developed shock and was treated with fluid resuscitation and inotropes. The patient developed subsequent multiorgan failure requiring dialysis. He had stayed in the intensive care unit for 12 days and needed another 3 weeks to fully recover [15]. We believe that this is the first reported case in the world of a patient with P. falciparum malaria and myocarditis that was supported successfully with ECMO until the malaria and sepsis resolved.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
All the authors were involved in the collection of data, writing of the manuscript and proof-reading the manuscript.

References