Severe Orthostatic Hypotension in Otherwise Uncomplicated Plasmodium Vivax Infection

Chaisith Sivakorn (chaisith.siv@mahidol.edu)
Mahidol University Faculty of Tropical Medicine https://orcid.org/0000-0001-5662-1058
Polrat Wilairatana
Mahidol University
Srivicha Krudsood
Mahidol University
Marcus J. Schultz
Amsterdam university
Tachpon Techarang
Walailak university
Khanittha kheawsawaung
Hospital for Tropical Diseases
Arjen M. Dondorp
MORU

Case report

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Abstract

Impaired autonomic control of postural homeostasis resulting in orthostatic hypotension has been described in falciparum malaria. However, severe orthostatic intolerance in *Plasmodium vivax* has not been previously reported. We describe a non-immune previously healthy Thai woman presenting with *Plasmodium vivax* infection with well-documented orthostatic hypotension. In addition to oral chloroquine and intravenous artesunate, the patient was treated with fluid resuscitation and norepinephrine. During hospitalization, her hemodynamic profile revealed orthostatic hypotension persisting for another three days after microscopic and polymerase chain reaction confirmed parasite clearance. Potential causes are discussed.

Background

Orthostatic hypotension is defined as a decrease in systolic blood pressure of 20 mmHg or a decrease in diastolic blood pressure of 10 mmHg within three minutes after a change from a reclining to upright posture, together with associated symptoms.[1] It can be a debilitating symptom in conditions characterized by autonomous nervous system dysfunction.[2]. Symptoms are caused by decreased cerebral perfusion, including blurred vision, fatigue, dizziness, and, in the most extreme cases, syncope.[3] On standing, the gravitational volume shift causes a redistribution of circulating blood, with pooling in the capacitance vessels below the diaphragm.[4] A normal compensatory hemodynamic response to changes in posture requires normal function of the cardiovascular, endocrine, and autonomic nervous systems.[1] Preservation of an adequate blood pressure is ensured by a prompt rise in cardiac output, mainly through an increase in heart rate, and an increase in vascular resistance favoring the cerebral blood circulation.[5] In dysautonomic states, this response to circulatory redistribution is impaired, which may lead to a compromised cerebral blood flow. Orthostatic hypotension in acute *Plasmodium falciparum* infection has been well described and is related to a combination of persisting relative bradycardia and insufficient peripheral vasoconstriction.[6] We present here a case of severe orthostatic hypotension in a patient with a *P. vivax* infection, mimicking severe malaria. Haemodynamic profiles and possible pathophysiological features are discussed.

Case Presentation

Patient is a 32-year old previously healthy Thai female without a history of malaria and not taking any medication before the disease episode. Two weeks prior to admission she had travelled to a malaria endemic forested area in Kanchanaburi Province, Thailand for camping and hiking with friends and her six-year-old son. Eight days prior to admission she developed a high-grade fever with headache and chills without localizing symptoms. On admission she had a fever of 39.8°C, a pulse rate of 78 beats per minute and a blood pressure of 90/60 mmHg. Her consciousness was normal, conjunctivae were not pale and sclerae were not icteric. She had no cold or clammy skin and her capillary refill time was less than 2 seconds. The liver span was ten centimeters in the mid-clavicular line and the spleen was normal in size on palpitation. Initial complete blood count revealed anemia with 31% hematocrit, as well as thrombocytopenia of 74,000/µL. Liver function tests revealed mild elevated aspartate aminotransferase and alanine aminotransferase of 60 U/L and 86 U/L, respectively. Blood sugar, creatinine, glucose-6-phosphate dehydrogenase (G6PD) enzyme activity and urinary analysis were normal. Microscopic examination of a peripheral blood film showed an asexual stage *Plasmodium* vivax parasitaemia of 69,800 parasites/µL and the diagnosis was confirmed by a positive polymerase chain reaction (PCR) for *P. vivax*. Initial inferior vena cava (IVC) collapsibility was 46%, which is predictive of a positive fluid responsiveness. She was admitted to the Hospital for Tropical Diseases and given 600 mg chloroquine orally and started on dextrose (5%)-saline (0.9%) infusion at a rate of 80 mL/hour. After ten hours and infusion of 800 ml fluids, the patient complained of postural faintness while getting out of bed. At that moment, she had an upright blood pressure of 77/46 mmHg and a pulse rate of 103 beats/ min. Her urine output was 0.5 to 1 ml/kg per an hour. After lying down, she had good consciousness, warm extremities and capillary refill less than 2 seconds. Her IVC collapsibility was 31%. Twelve-lead electrocardiogram showed sinus tachycardia with a normal QTc interval. She was diagnosed with severe *Plasmodium vivax* and given intravenous artesunate 2.4 mg/kg promptly followed by intravenous artesunate in the same dose after twelve hours, which was repeated every twenty-four hours for five days. Intravenous ceftriaxone was also started to cover potential concomitant bacterial septic shock awaiting blood culture results. Blood cultures obtained before start of antibiotics, however, remained without growth. After transferring the patient to the intensive care unit, 400 ml normal saline was given over one hour. After the fluid bolus her blood pressure remained 77/50 mmHg and her pulse rate was 72 beats/min while standing, increasing to 88/56 mmHg and 74 beats/min in the supine position, and IVC collapsibility of 16%, compatible with non-responsiveness to fluid resuscitation. Table 1 details her haemodynamic profiles during hospital admission. This prompted the start of intravenous norepinephrine at a dose of 0.13 ug/kg/min to maintain a blood pressure of 90/50 mmHg in an upright position. Her serum lactate assessed at that moment was 1.8 mmol/L (normal value: < 2 mmol/L). Her morning serum cortisol on the next day was 32 µg/dL (normal level: > 6 µg/dL) making a diagnosis of primary or secondary adrenal insufficiency unlikely, and corticosteroids were not started. Hemodynamic monitoring by an ultrasound cardiac output monitor (USCOM) in the supine and upright position before receiving norepinephrine showed a marked drop in cardiac index from 3 l/min/m^2 in the supine position to 1.9 l/min/m^2 after standing for three minutes, despite adequate hydration. The upright positional drop in cardiac output in the upright position was explained by an absence of an increase in stroke volume, and an insufficient increase in heart rate. (Table1) This orthostatic hypotension persisted until three days after microscopically confirmed parasite clearance, necessitating continued vasopressor support with norepinephrine (Table1) (Figure1-6). Orthostatic intolerance only resolved completely at the twelfth day of follow up.

Discussion

Orthostatic hypotension during an acute *P. falciparum* infection has been previously described[6] but not in *P. vivax.* This case report describes a five days episode of orthostatic hypotension in a non-immune Thai woman with vivax malaria after start of treatment with chloroquine and after adequate fluid resuscitation. Her orthostatic intolerance was unlikely to be caused by an underlying disease or medication. We did not consider the observed hypotension as a feature of severe malaria, since there were no signs of tissue hypoperfusion, with a normal plasma lactate concentration and normal capillary refill time, and no other indications of organ failure. She did receive low-dose vasopressor therapy, mainly to maintain an adequate blood pressure in an upright position. In falciparum malaria three potential mechanisms of orthostatic intolerance have been proposed. The first mechanism is autonomic dysfunction causing

relative bradycardia and impaired capacity to increase vascular resistance in the upright position, which will cause a drop in mainly the diastolic blood pressure in the upright position, as also observed in the presented case. In healthy young adults, the immediate response to a change in position from supine to upright is characterized by a prompt rise in heart rate of about 15 to 30%, and in total vascular resistance of 30 to 40%.[5] The main sensory receptors involved in the orthostatic neural reflex adjustment are the arterial mechanoreceptors (baroreceptors) located in the aortic arch and carotid sinuses and mechanoreceptors located in the heart and lungs (cardiopulmonary receptors). The cardiopulmonary receptors act in concert with the arterial baroreceptors to affect the necessary adjustment in sympathetic nerve action.[7] In patients with falciparum malaria, autonomic dysfunction causing an impaired neural reflex with insufficient compensatory tachycardia and arteriolar vasoconstriction is thought to be the primary cause of orthostatic hypotension in these patients.[8] and the subsequent increased subdiaphragmatic pooling of venous blood will subsequently cause a reduction in venous return resulting in a further reduction in stroke volume and thus cardiac output, exaggerating the orthostatic fall in blood pressure.

A second mechanism is blood flow redistribution due to venous vasodilation caused by fever and other factors,[9] with larger proportions of blood going to skin and muscle and decreased proportions to liver and kidney.[10] Combined with autonomic failure, this can further reduce venous return and thus cardiac output. Intravascular hypovolaemia can also contribute. Dehydration is common in patients with (falciparum) malaria, as illustrated by the frequently observed increase in the urea/creatinine ratio, increased plasma osmolarity and decreased fractional excretion of sodium, in the presence of an adequate antidiuretic hormone response.[11] Dehydration in patients with malaria is usually caused by transpiration, , vomiting or diarrhea, and inadequate fluid intake because of the acute illness. In our case, however, the patient had been adequately rehydrated, as illustrated by the normal IVC collapsibility index after fluid administration.

Chloroquine has also been described to cause hypotension[12, 13] and negative chronotropic effect.[14] Chloroquine decreases vascular resistance[15] through veno-vasodilation via the release of endothelial nitric oxide in the venous circulation .[16] Through vasodilatation, chloroquine may thus reduce both cardiac preload and afterload causing hypotension. Chloroquine also impairs adaptation of the heart rate via reduction in the firing of the spontaneous action potential of the so-called ‘funny current, causing bradycardia. [14] The oral administration of chloroquine could also have triggered an initial vasovagal reaction, but this would not explain the persisting orthostatic symptoms in our patient. Since her orthostatic symptoms persisted after parasite clearance, it is likely that chloroquine therapy contributed to the orthostatic hypotension in our patient, since chloroquine has a long plasma half-life, with an initial $t_{1/2}$ between 150 to 290 hours. [17] In the acute phase of her illness, the described factors which have been identified contributing to orthostatic hypotension in falciparum malaria could have played a role, but this is difficult to substantiate.

In conclusion, this case report shows that orthostatic hypotension may occur in patients with uncomplicated *P. vivax* infection. This could result from chloroquine therapy, whereas *P. vivax* induced autonomic dysfunction may also contribute.

Abbreviations

G6PD glucose-6-phosphate dehydrogenase

PCR polymerase chain reaction

IVC inferior vena cava

Declarations

Ethics approval and consent to participate

Exemption from obtaining ethics approval was granted due to a single case study and the patient was consented to participated in this study.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from Hospital for Tropical Diseases, but restrictions apply to the availability of these data and so are not publicly available. However, data are available from the authors upon reasonable request and with the permission of the institution.

Competing interests

Authors have no competing interests to declare.

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Authors’ contributions

CS, PW, AD and MS drafted the manuscript. CS and SK contributed in patient care. TT, KK contributed to facilitate in laboratory investigations.

All authors contributed to revise the manuscript. All authors approved the final version.

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Authors' information

[1]Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. [2]Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. [3]Mahidol–Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand. [4]Department of Intensive Care, and Laboratory of Experimental Intensive Care and Anesthesiology (L·E·I·C·A), Amsterdam University Medical Centers, location 'AMC', Amsterdam, The Netherlands. [5] Nuffield Department of Medicine, Oxford University, Oxford, United Kingdom. [6] School of Medicine, Walailak University, Nakhon Si Thammarat, Thailand. [7]Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

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Tables

Table1: Daily clinical data, laboratories and hemodynamic profiles.

Day of admission		Admission	Day 01		Day 02		Day 03		Day 04		Day 05	
Position		Supine	Supine	standing 3 minutes	Supine	Standing 3 minutes	Supine	standing 3 minutes	Supine	standing 3 minutes	Supine	stand 3 minu
Temperature (□c)		39.8	39.4		38		36.8		36.5		36.8	
Malaria	Microscopic exam (parasites/ μL)	430	155		62		negative		negative		negative	
	PCR	*Plasmodium vivax*	N/A		N/A		N/A		Negative for malaria		N/A	
Norepinephrine dose (μg/kg/min)		0	0.13		0.08		0.04		0.03		-	
Hemodynamic parameters	IVC maximum (cm)	1.23	1.72	N/A	1.57	N/A	1.73	N/A	1.38	N/A	1.13	N/A
	IVC minimum (cm)	0.66	1.18	N/A	1.23	N/A	1.38	N/A	1.03	N/A	0.84	N/A
	IVC collapsibility (%)	46.34	31.39	N/A	21.7	N/A	20.23	N/A	25.36	N/A	25.66	N/A
	Stroke Volume Index (ml/m²)	36	46	27	54	32	46	29	45	25	44	30
	Cardiac Index (l/min/m²)	2.7	3	1.9	3.2	2.3	3	2.4	3	2.3	3.4	2.6
Laboratories	Hematocrit (%)	31.2			26.3		26.9		27.2		28.9	
	Platelet (/ μL)	74,000			68,000		117,000		158,000		213,000	
	AST/ALT (U/L)	60/86			40/62		105/160		-/-		80/154	
	Lactate (mmol/L)	1.8			1.3		0.99		-		-	
Intake/output		1,584/1,100			3248/1618		2761/3630		1593/2335		1387/1860	

Abbreviations : PCR, polymerase chain reaction; IVC, inferior vena cava; AST, aspartate aminotransferase; ALT, alanine aminotransferase; N/A, not available

IVC collapsibility = (maximum diameter – minimum diameter) / (maximum diameter) x 100

Figures

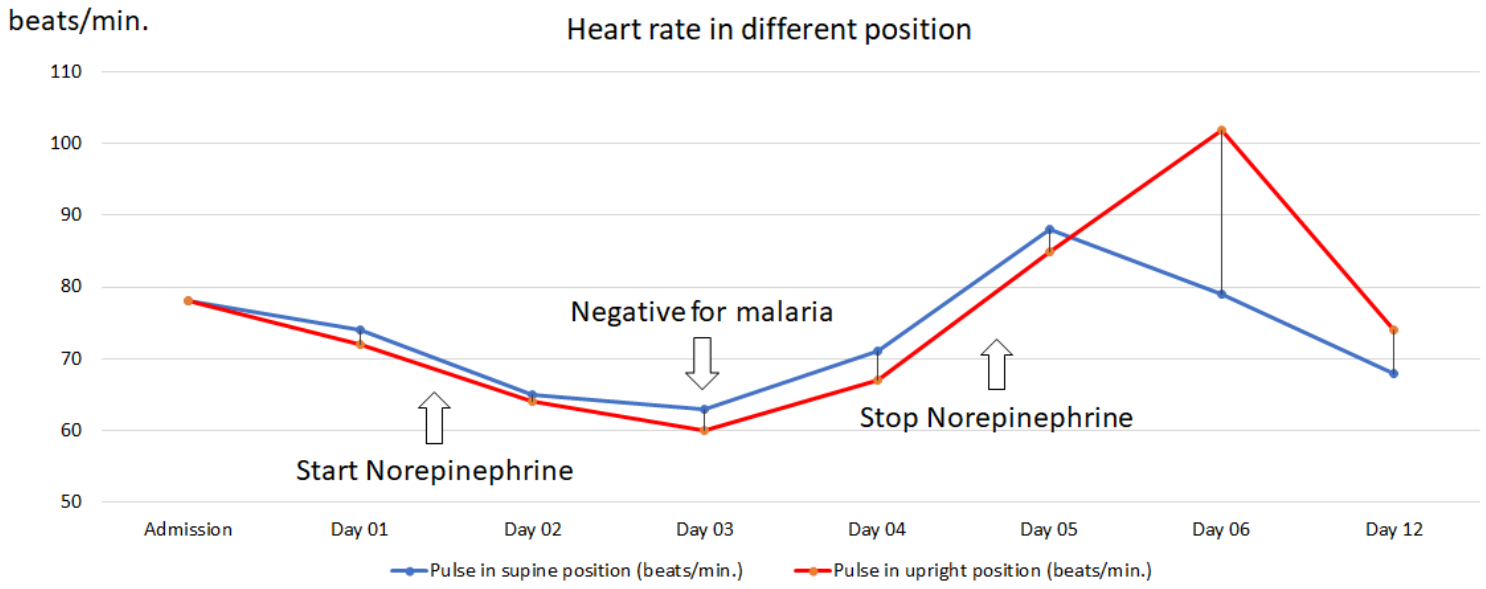

Figure 1 : Heart rate in supine position (blue line) and standing for three minutes position (red line)

Figure 1

Daily Heart rate in supine and standing for three minutes position

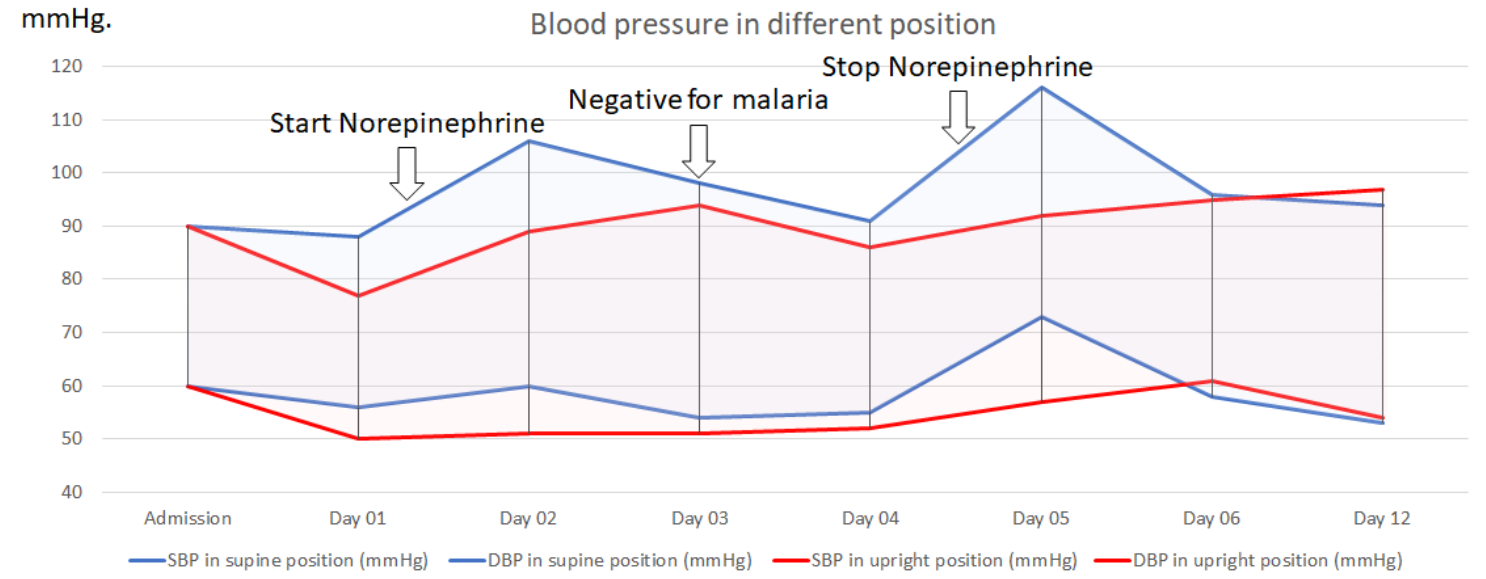

Figure 2: Systolic blood pressure (SBP) and diastolic blood pressure (DBP) in supine position (blue line) and standing for three minutes position (red line)

Figure 2

Daily systolic blood pressure and diastolic blood pressure in supine position and standing for three minutes position

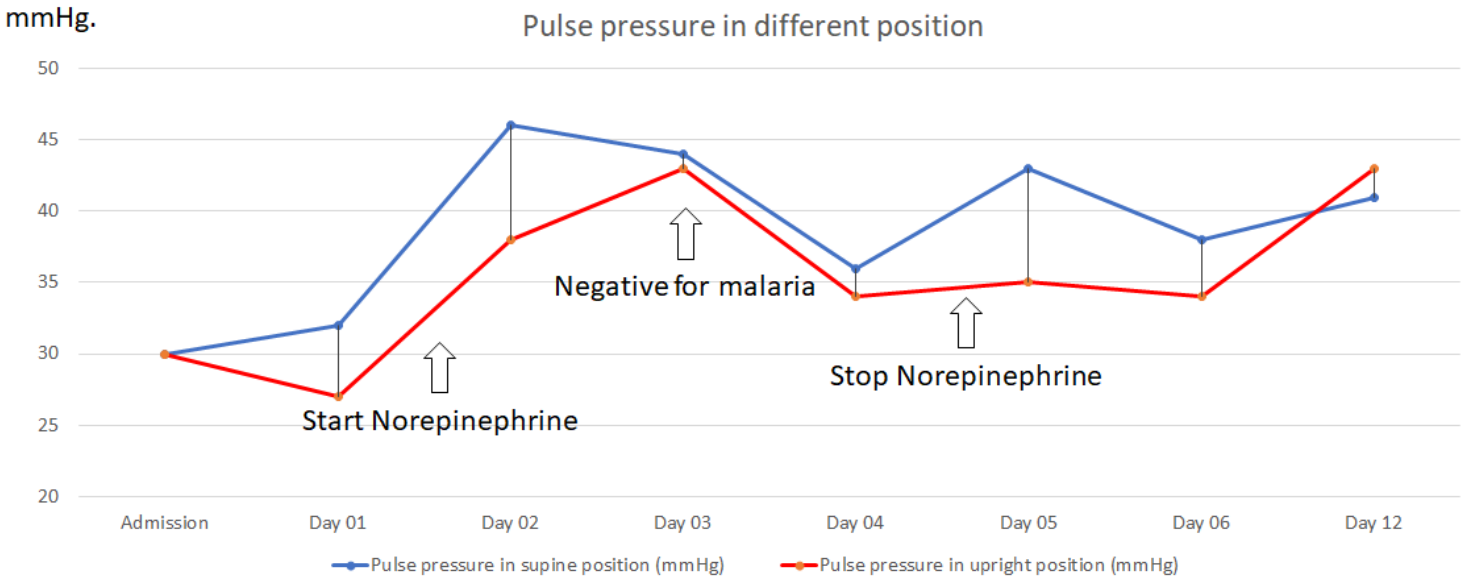

Figure 3: Pulse pressure in supine position (blue line) and standing for three minutes position (red line)

Figure 3

Daily pulse pressure in supine position and standing for three minutes position

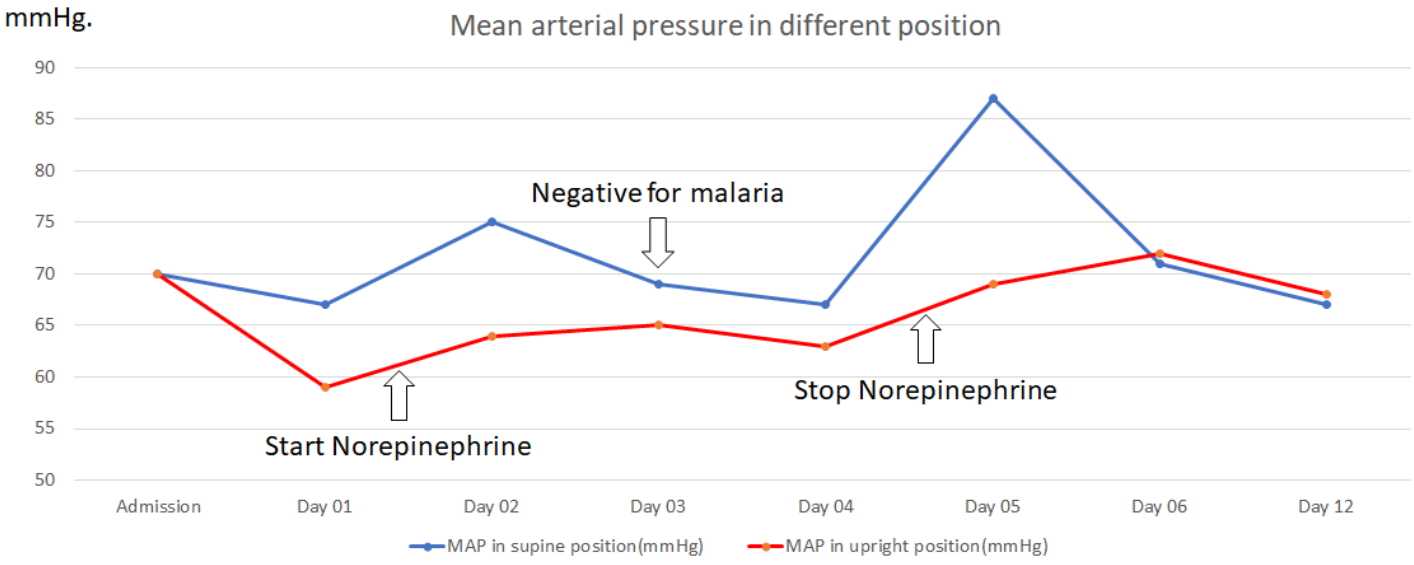

Figure 4: Mean arterial pressure (MAP) in supine position (blue line) and standing for three minutes position (red line)

Figure 4

Daily mean arterial pressure in supine position and standing for three minutes position

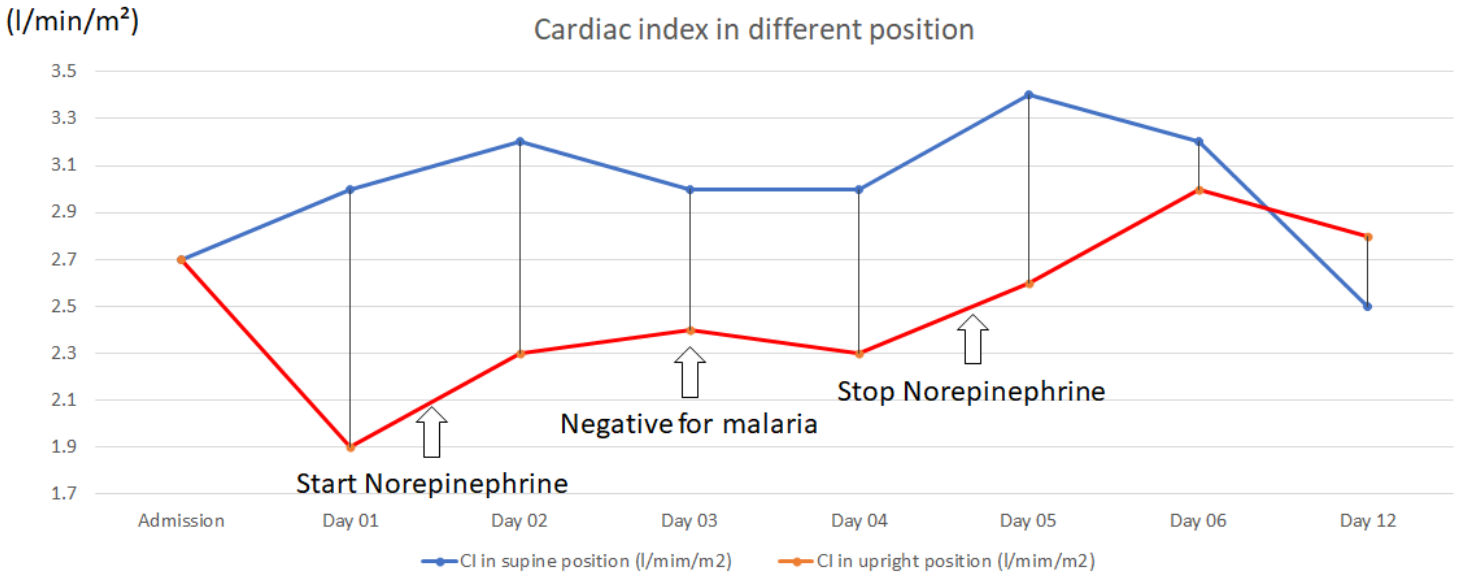

Figure 5: Cardiac index (CI) in supine position (blue line) and standing for three minutes position (red line)

Figure 5

Daily cardiac index in supine position and standing for three minutes position

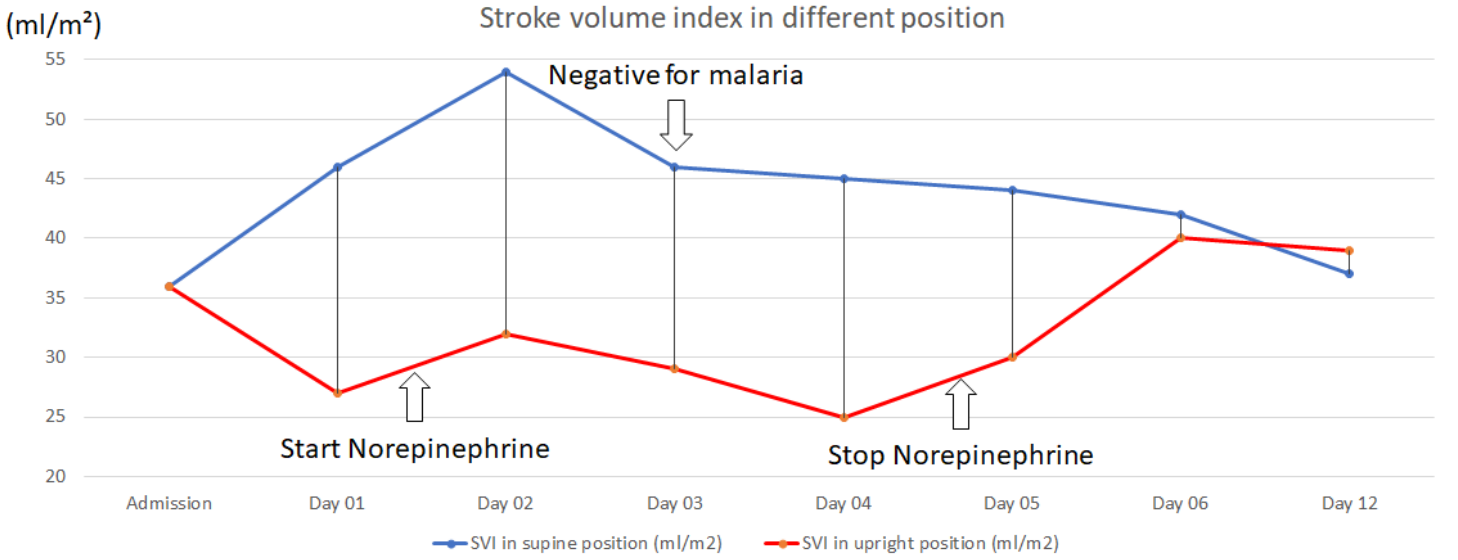

Figure 6: Stroke volume index (SVI) in supine position (blue line) and standing for three minutes position (red line)

Figure 6

Daily stroke volume index in supine position and standing for three minutes position