

The Effects of Malnutrition on Cardiac Function in African Children

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Abstract

The Effects of Malnutrition on Cardiac Function in African Children

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Objective:

To assess the effect of malnutrition on cardiac function in hospitalized African children.

Design:

Prospective cross-sectional study.

Setting:

Public referral hospital in Blantyre, Malawi.

Patients:

We enrolled 272 stable, hospitalized children ages 6-59 months, with and without WHO-defined severe acute malnutrition.

Main outcome measures:

Cardiac index, heart rate, mean arterial pressure, stroke volume index, and systemic vascular resistance index were measured by the Ultrasound Cardiac Output Monitor (USCOM, Ltd, NSW, Australia). We used linear regression with generalized estimating equations controlling for age, sex, and anemia.

Results:

Our primary outcome, cardiac index, was similar between those with and without severe malnutrition: $\beta=0.17$ L/min/m², (95% CI: -0.17, 0.51 L/min/m²). No difference was found in

heart rate or stroke volume index. However, mean arterial pressure and systemic vascular resistance index were lower in children with severe malnutrition: $\beta = -8.6$ mm Hg (95% CI: -12.7, -4.6 mm Hg) and $\beta = -200$ dyne s/cm⁵/m² (95% CI: -320, -80 dyne s/cm⁵/m²), respectively.

Conclusions:

In this largest study to date of cardiac function in malnourished children we found that that cardiac function is preserved in stable, hospitalized subjects. Lower mean arterial pressure and systemic vascular resistance index may indicate that these children are in a hypermetabolic state due to early effects of refeeding. Further study is needed to determine if cardiac function is diminished in unstable malnourished children.

Background:

Despite technologic advances in food production, malnutrition remains a major cause of global childhood morbidity and mortality. It is estimated that malnutrition affects well over 150 million children worldwide and is associated with 45% of all child deaths.(1) Malnutrition-related mortality is primarily related to infection or dehydration, but often there is no identifiable cause of death.(2, 3) Some researchers have proposed that cardiac dysfunction may be associated with these unexplained deaths either directly or through decompensation after aggressive fluid resuscitation.(4-6) While there is consensus that heart size reduces in proportion to body mass in malnourished children, there have been conflicting findings regarding cardiac function.

Some studies have found that while cardiac function is impaired, the reduction is appropriate and proportional to the decrease in body surface area (BSA), which is an indicator of overall metabolic demand.(7-13) Others studies have found that cardiac function is impacted pathologically in the malnourished child and decreases disproportionately to BSA.(14-19) A third possibility is that in stable malnourished children, heart function is adequate, but in the setting of stress, the most severely affected children decompensate more readily than their better nourished counterparts.(7, 13, 14)

There are many different indicators of heart function. In resource-limited settings, physical exam findings such as pulse rate and quality, blood pressure, and capillary refill time are used most commonly, though these can be subjective, associated with significant inter-recorder variability,(20) and may be dependent on metabolic state.(4) More sophisticated measures may

be obtained by ultrasonography, echocardiography, or invasive dye dilution techniques, but are often unavailable in the developing world. The Ultrasound Cardiac Output Monitor (USCOM Ltd, Sydney, Australia) is a non-invasive, point of care, continuous wave Doppler ultrasound device. It has been used extensively in clinical practice and validated for research,(21) though it has not yet been used in malnourished children. Unlike echocardiography, it is easily employed by both physicians and nurses and has been shown to be reliable after 20 practice scans.(22-24) Reported parameters include heart rate, stroke volume index, cardiac output, cardiac index, systemic vascular resistance index, and Smith-Madigan Inotropy Index.

The stroke volume is the amount blood ejected with each contraction of the heart. The cardiac output is the amount of blood pumped by the heart in a minute and is the product of the stroke volume x heart rate. Dividing the cardiac output by the BSA, one obtains the cardiac index, which standardizes the cardiac output to the size and metabolic demands of the child and is relatively constant with increasing age(25). The systemic vascular resistance index is the mean arterial pressure divided by the cardiac index and represents the afterload against which the heart pumps blood. A novel parameter, the Smith-Madigan Inotropy Index measures the overall work of the heart, standardized to BSA. This incorporates the kinetic energy (blood flow) with the potential energy (change in blood pressure) generated with each beat of the heart. This may be a better measure of contractility and overall heart function, as it controls for variation in the cardiac index in low vs. high systemic vascular resistance states.(26) However, it requires further validation.

The objective of our study was to assess for differences in cardiac function among stable, hospitalized children with and without severe acute malnutrition using the USCOM.

Methods:

Data Collection

We conducted a prospective cross-sectional study of cardiac function in children ages 6-59 months admitted to the pediatric wards at Queen Elizabeth Central Hospital in Blantyre, Malawi from November 2013 through March 2014. All children admitted to either the general ward or the malnutrition ward were considered for inclusion in the study, based on availability of the study nurse. Written informed consent was obtained from the parent prior to enrollment.

In order to minimize bias from clinical states that might transiently alter a subject's cardiovascular physiology and to ensure that both malnourished and non-malnourished children had similar disease severity, we excluded children with 1) known or suspected heart or disease, 2) temperature of 38 degrees C or higher, 3) more than 3 watery stools in the last 24 hours, 4) dry mouth or eyes 5) no urine output in the last 8 hours 6) chest indrawing 7) tachypnea, or 8) need for supplemental oxygen. Patients with a diagnosis of nephrotic syndrome were also excluded to avoid misclassification due to edema status. Patients who may have been initially excluded due one of the criteria above could be reevaluated for inclusion on a subsequent day and enrolled if eligible upon reexamination.

The study nurse performed a physical examination at the time of enrollment, documenting heart rate, respiratory rate, automated blood pressure, capillary refill time, hydration and respiratory status, edema, and anthropometrics (weight, height, mid-upper arm circumference (MUAC)). Relevant clinical information such as admission diagnosis, duration of stay at time of enrollment, IV fluid and medication administration, HIV status (if known), and laboratory data were extracted from the patient's medical chart. We defined anemia as hemoglobin less than 8 or hematocrit or packed cell volume (PCV) less than 24 on most recent measurement. In those who were transfused but did not have post-transfusion values, we extrapolated their likely hemoglobin or PCV by adding 1 g/dL or 3% for each 10 mL/kg of packed cells transfused to the pre-transfusion value.

Multiple USCOM measurements of cardiac index, cardiac output, heart rate, stroke volume index, systemic vascular resistance index, and Smith-Madigan Inotropy Index were obtained at the time of enrollment. Measurements were made using a 2.2 MHz probe applied over the child's suprasternal notch to obtain a Doppler ultrasound measurement of aortic blood flow. In some cases adequate tracings were not obtainable due to poor patient cooperation, and these were subsequently excluded. Blood pressure was measured with an automated pediatric sphygmomanometer (Contec Medical Systems Co., Pty., Qinhuongdao, China).

For our primary analysis, we defined severe acute malnutrition (SAM) according to WHO median reference values: weight:length < -3 standard deviations (SD) or Z scores from median; and/or mid-upper arm circumference < 11.5 cm; and/or bilateral pedal edema.(27) Our primary

outcome variable was cardiac index. In our secondary analysis we categorized patients by degree of wasting: $wt:ht \geq -2$ SD; -2 SD $> wt:ht \geq -3$ SD; 3 SD $> wt:ht \geq -4$ SD; or $wt:ht < -4$ SD.

We estimated that a sample size of 244 children with 122 each in the SAM and non-SAM groups, would result in 80% power to detect a 7% change in cardiac index with an alpha of 0.05.

Statistical Analysis

Our data was de-identified and collated in Excel (Microsoft, Redmond, WA) spreadsheets. We used Stata 12.1 (College Station, TX) for analysis. We performed linear regression with generalized estimating equations and exchangeable correlation matrices to determine the effect of malnutrition on various cardiovascular indices. Covariates included in the multivariable analyses were selected *a priori* and included age, sex, and anemia status. For our secondary analysis where wasting was stratified by Z score, we also controlled for the presence or absence of edema.

This study was approved by the Malawi College of Medicine Research Ethics Committee. “Non-engaged” status was determined by the University of Washington IRB.

Results:

We identified 272 children who met inclusion criteria, (161 severely malnourished and 111 not severely malnourished) and analyzed 1019 USCOM studies (median 3 studies/subject). Five children were excluded because of erroneous clinical data. Baseline characteristics were similar

between severely malnourished and non-severely malnourished, with the exception of HIV prevalence, which was higher among those with SAM (Tables 1a and 1b). In our primary analysis we found that the cardiac index was similar between groups: $\beta=0.22$ L/min/m² (95% CI -0.08, 0.51 L/min/m²) (Table 2), while the cardiac output was significantly lower in those with SAM: $\beta=0.34$ L/min (95% CI: -0.54, -0.07 L/min) (Table 3a). Both mean arterial blood pressure and systemic vascular resistance indices decreased significantly with SAM. When stratified by wasting in secondary analysis, we found that cardiac index and stroke volume were significantly higher in the most wasted children (Table 3b). Both mean arterial blood pressure and systemic vascular resistance indices decreased with SAM. As in the primary analysis, when stratified by wasting, blood pressure and systemic vascular resistance index decreased with worsening nutritional status. However, heart rate and Smith-Madigan Inotropy Index were similar between the two groups.

Table 1a. Baseline characteristics of Malawian children aged 6-59 months, dichotomized by WHO severe acute malnutrition status

Characteristics Median (IQR), unless otherwise specified	Not Severely Malnourished n=111	Severely Malnourished n=161
Age in months	20 (13, 33)	21 (14, 28)
Female n (%)	46 (41)	66 (41)
Hospital day at time of exam	3 (2, 3)	4 (2, 6)
Anemic ^a (%)	9 (10) ^b	16 (14) ^c
HIV + (%)	3 (4) ^d	34 (27) ^e
Mid-upper arm circumference	14.5 (13.5, 15.4)	11.8 (10.8, 13.0)
Wt/Ht Z Score	-1.2 (-1.9, -0.3)	-3.3 (-4.1, -1.7)
Ht/Age Z Score	-1.0 (-2.0, 0.6)	-2.8 (-3.8, -1.6)
Marasmic (% of severely malnourished)	---	69 (43)
Marasmic kwashiorkor (% of severely malnourished)	---	39 (24)
Kwashiorkor (% of severely malnourished)	---	53 (33)

^aAnemia defined as hemoglobin \leq 8 or packed cell volume \leq 24

^bn=87 where anemia status known

^cn=116 where anemia status known

^dn=76 where HIV status known

^en=126 where HIV status known

Table 1b. Baseline characteristics of study subjects stratified by wt:ht Z score

Characteristics Median (IQR), unless otherwise specified	Wt:ht \geq -2 SD n=132	-2 SD > Wt:ht \geq -3 SD n=46	-3 SD > Wt:ht \geq -4 SD n=48	Wt:ht < -4 SD n=46
Age in months	21 (13, 33)	23 (15, 30)	18 (13, 27)	21 (17, 28)
Female n (%)	57 (43)	16 (35)	23 (48)	16 (35)
Hospital day at time of exam	3 (2,4)	3 (2,4)	4 (2,6)	4 (2, 6)
Anemic ^a (%)	10 (9) ^b	7 (19) ^c	5 (17) ^d	3 (10) ^e
HIV + (%)	6 (6) ^f	4 (11) ^g	12 (32) ^h	15 (47) ⁱ
Mid-upper arm circumference	14 (13, 15)	13 (12, 14)	12 (11,12)	11 (10, 11.5)
Wt/Ht Z Score	-0.8 (-1.5, -0.1)	-2.5 (-2.8, -2.3)	-3.5 (-3.7, -3.3)	-4.6 (-5.2, -4.2)
Ht/Age Z Score	-1.5 (-2.8, 0.1)	-1.7 (-3.3, -1.1)	-2.7 (-3.3, -1.2)	-3 (-4.2, -2)
Marasmic (% of severely malnourished)	4 (3)	4 (9)	33 (69)	28 (61)
Marasmic kwashiorkor (% of severely malnourished)	2 (2)	4 (9)	15 (31)	18 (39)
Kwashiorkor (% of severely malnourished)	41 (31)	12 (26)	0 (0)	0 (0)

^aAnemia defined as hemoglobin \leq 8 or packed cell volume \leq 24

^bn= 107 where anemia status known

^cn= 36 where anemia status known

^dn=30 where anemia status known

^en=30 where anemia status known

^fn=98 where HIV status known

^gn=35 where HIV status known

^hn=37 where HIV status known

ⁱn=32 where HIV status known

Table 2. Summary of univariable and multivariable-adjusted determinants for cardiac index among N=272 children.

	Univariable			Multivariable 1 ^a			Multivariable 2 ^b		
	β	95% CI	<i>P</i>	β	95% CI	<i>P</i>	β	95% CI	<i>P</i>
Female	0.05	-0.25, 0.35	.75	0.05	-0.25, 0.35	.73	0.08	-0.22, 0.37	.62
Age (months)	0.00	-0.01, 0.01	.91	0.00	-0.01, 0.01	.93	0.00	-0.01, 0.01	.95
Edema	-0.16	-0.33, 0.29	.92	---	---	---	-0.05	-0.36, 0.26	.78
Anemia	0.05	-0.12, 0.22	.54	0.04	-0.13, 0.21	.61	0.01	-0.16, 0.18	.88
WHO severe malnutrition ^c	0.22	-0.08, 0.52	.14	0.22	-0.08, 0.51	.16	---	---	---
Malnutrition category									
Wt:ht \geq -2 SD	Ref.	---	---	---	---	---	Ref.	---	---
-2 SD $>$ Wt:ht \geq -3 SD	0.18	-0.23, 0.59	.39	---	---	---	0.18	-0.23, 0.59	.38
-3 SD $>$ Wt:ht \geq -4 SD	0.28	-0.12, 0.68	.17	---	---	---	0.27	-0.14, 0.68	.20
Wt:ht $<$ -4 SD	0.66	0.25, 1.07	.002	---	---	---	0.67	0.25, 1.08	.002

^a adjusted for age, sex, anemia with exposure of interest being WHO severe malnutrition

^b adjusted for age, sex, anemia and edema with exposure of interest being wasting (malnutrition), stratified by Z-score or SD

^c wt:ht $<$ -3 SD and/or MUAC $<$ 11.5 and/or edema

Table 3a. Change in multivariable adjusted cardiac parameters (95% CI) among N=272 dichotomized by WHO Severe Acute Malnutrition Status*

	Cardiac Output in L/min	Smith-Madigan Inotropy Index W/m ²	Stroke Volume Index in mL/beat/m ²	Heart Rate in beats/min	Mean Arterial Pressure in mm Hg	Systemic Vascular Resistance Index in dyne s/cm ⁵ /m ²
WHO Severe Acute Malnutrition absent	ref	ref	ref	ref	ref	ref
WHO Severe Acute Malnutrition present	-0.34 (-0.50, -0.18)	-0.11 (-0.23, 0.01)	0.89 (-1.43, 3.21)	0.04 (-3.93, 4.00)	-8.62 (-12.67, -4.58)	-200 (-320, -80)
Constant	1.84 (1.54, 2.14)	1.64 (1.41, 1.87)	36.41 (31.96, 40.87)	137.33 (129.71, 144.94)	78.02 (70.26, 85.79)	1647 (1417, 1877)

* Adjusted for age, sex, and anemia status

Table 3b. Change in multivariable adjusted cardiac parameters (95% CI) among N=272 stratified by Z score**

	Cardiac Output in L/min	Smith-Madigan Inotropy Index in W/m ²	Stroke Volume Index in mL/beat/m ²	Heart Rate in beats/min	Mean Arterial Pressure in mm Hg	Systemic Vascular Resistance Index in dyne s/cm ⁵ /m ²
Wt:ht ≥ -2 SD	ref	ref	ref	ref	ref	ref
-2 SD > Wt:ht ≥ -3 SD	-0.13, (-0.35, 0.08)	-0.08 (-0.24, 0.08)	2.84 (-0.31, 5.99)	0.90 (-4.58, 6.38)	-6.78 (-12.37, -1.18)	-197 (-360, -34)
-3 SD > Wt:ht ≥ -4 SD	-0.30, (-0.54, -0.07)	-0.01 (-0.17, 0.16)	1.78 (-1.37, 4.94)	2.27 (-3.21, 7.74)	-5.19 (-10.77, 0.40)	-191 (-355, -28)
Wt:ht < -4 SD	-0.32 (-0.55, -0.08)	0.09 (-0.08, 0.26)	5.62 (2.43, 8.80)	2.94 (-2.58, 8.46)	-11.02 (-16.65, -5.40)	-346 (-511, -181)
Constant	1.95 (1.59, 2.31)	1.77 (1.51, 2.03)	35.36 (30.26, 40.46)	139.96 (131.12, 148.81)	77.16 (69.49, 84.83)	1736 (1472, 2000)

** adjusted for age, sex, anemia status, and edema

We performed a sensitivity analysis to assess whether inpatient length of stay at time of assessment may have affected our findings, and we found no effect on cardiac index. Excluding those with hospital length of stay more than 5 days at time of assessment, we still found no change in cardiac index. In another sensitivity analysis, we found that HIV seropositivity had no impact on cardiac index. We observed that there was a 10% mortality rate in those with WHO SAM and 0% mortality in those without. A sensitivity analysis excluding those who died or who were missing data on status at discharge showed no difference in cardiac index.

Discussion:

To our knowledge this is the largest study of cardiac function in malnourished children. We found that cardiac index was similar in children with and without severe malnutrition. This suggests that cardiac output in malnourished children is reduced in proportion to BSA. Our study is the first to use USCOM, a non-invasive technology, to assess heart function in malnourished children and the first to use the Smith-Madigan Inotropy Index as a measure of cardiac work in this group. Several studies employing echocardiography have similarly found no difference in cardiac index, shortening fraction, and ejection fraction when comparing children with and without malnutrition.(7, 10-13) Of note, one study of Indian children showed a statistically significant increase in cardiac index in malnourished children compared to non-malnourished controls.(13)

When we stratified by level of wasting in our secondary analysis, we found that cardiac index was higher in the most severely wasted children ($wt:ht < -4$ SD). Cardiac index is determined by

the heart rate, myocardial contractility or inotropy, preload, and afterload. We found no difference in the heart rate or Smith Madigan Inotropy Index between groups. Although we were unable to measure preload, we excluded patients with signs of dehydration, shock or heart failure on clinical examination in both groups, so preload was likely adequate in both groups. Therefore, the most likely driver of the increased cardiac index in our most wasted patients was a reduced afterload, as indicated by the lower mean arterial pressure and systemic vascular resistance index we found in our most wasted patients.

One possible driver for this increased cardiac index and decreased systemic vascular resistance index in the most severely wasted is the hyperdynamic state associated with recovery from malnutrition. In a study of malnourished adults, cardiac output normalized by body weight increased quickly with oral and IV hyperalimentation.(28) The findings were attributed to the hyperdynamic state associated with hyperalimentation.(29) A similar rise in cardiac output upon refeeding was seen in studies of malnourished Jamaican and Thai children.(18, 19) Given that most children in our study were examined on hospital day 3 or 4, it is possible that subjects were already in a hyperdynamic recovery period. This may explain why we found a dose response pattern with increasing cardiac index and stroke volume and decreasing blood pressure and systemic vascular resistance index with higher degrees of wasting. On the other hand, we found no change in cardiac index when stratifying by duration of hospitalization and refeeding prior to examination. It should also be noted that our findings are not consistent with classical “refeeding syndrome,” whereby fluid and electrolyte shifts are associated with heart failure upon refeeding, with patients manifesting tachycardia, increased systemic vascular resistance, and decreased

stroke volume.(30) Such patients would have likely been excluded from our study due to their hemodynamic instability.

In contrast to the increased cardiac function observed in nutritional recovery, other studies observed worse systolic function in the malnourished.(16, 17) Of note, one study in Zaire using pulmonary artery catheterizations found a 58% reduction in cardiac index when comparing ill malnourished children to healthy controls. In contrast to the children in our study, these malnourished subjects were more often in a hypocirculatory state on presentation with cold extremities, delayed capillary refill time and bradycardia. Many of these children later died. This reduction in cardiac function in severely ill, malnourished patients suggests that there may be some threshold of illness beyond which cardiac dysfunction becomes apparent.(14, 15) Importantly, patients with signs of shock, such as those seen in Zaire, would have been excluded from our study.

Limitations:

Our study has several limitations. Obtaining USCOM measurements on small and often uncooperative children was technically challenging. However, since the nurse performed the studies in both comparison groups, it is unlikely that this would have affected the differences between groups. Another technical limitation to our study is that we used weight at time of examination to categorize our patients by malnutrition status. It may have been better to use nadir weights, since the degree of wasting in children presenting with kwashiorkor can be underestimated until their edema resolves. This would not have affected our comparison of

severely malnourished to non-severely malnourished children, but may have biased our results towards the null between when stratified by severity of wasting.

It is also possible that the nomogram which estimates aortic outflow tract diameter used by the USCOM software, based on height,(31) over or underestimates this parameter in the malnourished. However, the investigators found that adding BSA or weight to the model did not improve accuracy over height alone. This is reassuring that the presence of wasting would not limit the application of the nomogram to our study population. Future studies could obtain echocardiograms in a subset of patients to validate USCOM measurements in the malnourished.

While the USCOM has been validated in many settings,(21-23) some studies have questioned the accuracy of the device compared to echocardiography and pulmonary artery catheterization.(24, 32, 33) However, since the goal of our study was to seek differences in cardiac parameters between groups, the absolute accuracy of the measurements should not impact the validity of our findings.

We excluded unstable children to minimize confounding by disease severity. However since more of the severely malnourished children ultimately died, they may have been more ill at baseline. When we excluded children who died in a sensitivity analysis, however, we still found no differences between the groups. Since our study was conducted at a referral hospital, it is possible that our children were more ill or medically complex than would be seen at a primary or district level facility, which may limit generalizability.

We used cardiac index (cardiac output normalized by BSA) to compare groups since BSA is often used as a marker for metabolic demand. However, it is unclear if calculated BSA correlates with metabolic demand, particularly in malnourished children and non-caucasians.(34-37) Even if we put aside whether or not BSA accurately measures metabolic demand in our population, the more relevant question may be whether these children have adequate cardiac function for their needs, which may be adaptively minimized in the malnourished state and whether their hearts could withstand an acute physiologic stressor.

In summary, we did not observe significant differences in cardiac index of stable hospitalized Malawian children with and without severe acute malnutrition, though the subset of most severely wasted children (wt:ht <-4 SD) demonstrated higher mean cardiac index, likely as a result of decreased afterload. Additional studies of cardiac function in acutely-ill malnourished children are required to better understand how best to resuscitate these fragile children and improve their chances of survival.

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References

1. Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet*. 2013;382:427-51 doi: 10.1016/s0140-6736(13)60937-x.
2. Smythe PM, Swanepoel A, Campbell JA. The heart in kwashiorkor. *British medical journal*. 1962;1:67-73.

3. Brewster DR. Critical appraisal of the management of severe malnutrition: 3. Complications. *Journal of paediatrics and child health*. 2006;42:583-93 doi: 10.1111/j.1440-1754.2006.00933.x.
4. Organization WH. Management of severe malnutrition: a manual for physicians and other senior health workers. 1999.
5. Akech SO, Karisa J, Nakamya P, Boga M, Maitland K. Phase II trial of isotonic fluid resuscitation in Kenyan children with severe malnutrition and hypovolaemia. *BMC pediatrics*. 2010;10:71 doi: 10.1186/1471-2431-10-71.
6. Webb JG, Kiess MC, Chan-Yan CC. Malnutrition and the heart. *CMAJ: Canadian Medical Association Journal*. 1986;135:753-8.
7. El-Sayed HL, Nassar MF, Habib NM, Elmasry OA, Gomaa SM. Structural and functional affection of the heart in protein energy malnutrition patients on admission and after nutritional recovery. *European journal of clinical nutrition*. 2006;60:502-10 doi: 10.1038/sj.ejcn.1602344.
8. Bergman JW, Human DG, De Moor MM, Schulz JM. Effect of kwashiorkor on the cardiovascular system. *Archives of disease in childhood*. 1988;63:1359-62.
9. Singh GR, Malathi KE, Kasliwal RR, Ommar A, Padmavati S, Ramji S. An evaluation of cardiac function in malnourished children by non-invasive methods. *Indian pediatrics*. 1989;26:875-81.
10. Shoukry I, Shoukry A, Ibrahim MM, Fahmy N, Madkour MA, El Said G. Cardiac Atrophy and Ventricular Function in Infants with Severe Protein Calorie Malnutrition (Kwashiorkor Disease). In: Doyle E, Engle M, Gersony W, Rashkind W, Talner N, eds. *Pediatric cardiology*: Springer New York 1986:1169-71.
11. Olivares JL, Vázquez M, Rodríguez G, Samper P, Fleta J. Electrocardiographic and Echocardiographic Findings in Malnourished Children. *Journal of the American College of Nutrition*. 2005;24:38-43 doi: 10.1080/07315724.2005.10719441.
12. Ocal B, Unal S, Zorlu P, Tezic HT, Oguz D. Echocardiographic evaluation of cardiac functions and left ventricular mass in children with malnutrition. *Journal of paediatrics and child health*. 2001;37:14-7.
13. Kothari SS, Patel TM, Shetalwad AN, Patel TK. Left ventricular mass and function in children with severe protein energy malnutrition. *International journal of cardiology*. 1992;35:19-25.
14. Viart P. Hemodynamic findings in severe protein-calorie malnutrition. *The American journal of clinical nutrition*. 1977;30:334-48.
15. Viart P. Hemodynamic findings during treatment of protein-calorie malnutrition. *The American journal of clinical nutrition*. 1978;31:911-26.
16. Olowonyo MT, Akinbami FO, Ogunkunle OO, Jaiyesimi F. The electrocardiographic changes in kwashiorkor. *Annals of tropical paediatrics*. 1993;13:293-8.
17. Keys A, Henschel A, Taylor HL. The size and function of the human heart at rest in semi-starvation and in subsequent rehabilitation. *The American journal of physiology*. 1947;150:153-69.
18. Alleyne GA. Cardiac function in severely malnourished Jamaican children. *Clinical science*. 1966;30:553-62.
19. Phornphatkul C, Pongprot Y, Suskind R, George V, Fuchs G. Cardiac function in malnourished children. *Clinical pediatrics*. 1994;33:147-54.

20. Otieno H, Were E, Ahmed I, Charo E, Brent A, Maitland K. Are bedside features of shock reproducible between different observers? *Archives of disease in childhood*. 2004;89:977-9 doi: 10.1136/adc.2003.043901.
21. Cattermole GN, Leung PY, Mak PS, Chan SS, Graham CA, Rainer TH. The normal ranges of cardiovascular parameters in children measured using the Ultrasonic Cardiac Output Monitor. *Critical care medicine*. 2010;38:1875-81 doi: 10.1097/CCM.0b013e3181e8adee.
22. Dey I, Sprivulis P. Emergency physicians can reliably assess emergency department patient cardiac output using the USCOM continuous wave Doppler cardiac output monitor. *Emergency medicine Australasia : EMA*. 2005;17:193-9 doi: 10.1111/j.1742-6723.2005.00722.x.
23. Corley A, Barnett AG, Mullany D, Fraser JF. Nurse-determined assessment of cardiac output. Comparing a non-invasive cardiac output device and pulmonary artery catheter: a prospective observational study. *International journal of nursing studies*. 2009;46:1291-7 doi: 10.1016/j.ijnurstu.2009.03.013.
24. Wongsirimetheekul T, Khositseth A, Lertbunrian R. Non-invasive cardiac output assessment in critically ill paediatric patients. *Acta cardiologica*. 2014;69:167-73.
25. Krovetz LJ. The physiologic significance of body surface area. *The Journal of pediatrics*. 1965;67:841-62.
26. Smith BE, Madigan VM. Non-invasive method for rapid bedside estimation of inotropy: theory and preliminary clinical validation. *British journal of anaesthesia*. 2013;111:580-8 doi: 10.1093/bja/aet118.
27. Guideline: Updates on the Management of Severe Acute Malnutrition in Infants and Children. Geneva: World Health Organization 2013.; 2013.
28. Heymsfield SB, Bethel RA, Ansley JD, Gibbs DM, Felner JM, Nutter DO. Cardiac abnormalities in cachectic patients before and during nutritional repletion. *American heart journal*. 1978;95:584-94.
29. Heymsfield SB, Head CA, McManus CB, 3rd, Seitz S, Staton GW, Grossman GD. Respiratory, cardiovascular, and metabolic effects of enteral hyperalimentation: influence of formula dose and composition. *The American journal of clinical nutrition*. 1984;40:116-30.
30. Fuentebella J, Kerner JA. Refeeding syndrome. *Pediatric clinics of North America*. 2009;56:1201-10 doi: 10.1016/j.pcl.2009.06.006.
31. Nidorf SM, Picard MH, Triulzi MO, et al. New perspectives in the assessment of cardiac chamber dimensions during development and adulthood. *Journal of the American College of Cardiology*. 1992;19:983-8.
32. Thom O, Taylor DM, Wolfe RE, et al. Comparison of a supra-sternal cardiac output monitor (USCOM) with the pulmonary artery catheter. *British journal of anaesthesia*. 2009;103:800-4 doi: 10.1093/bja/aep296.
33. Chong SW, Peyton PJ. A meta-analysis of the accuracy and precision of the ultrasonic cardiac output monitor (USCOM). *Anaesthesia*. 2012;67:1266-71 doi: 10.1111/j.1365-2044.2012.07311.x.
34. Gibson S, Numa A. The importance of metabolic rate and the folly of body surface area calculations. *Anaesthesia*. 2003;58:50-5.
35. Chhapola V, Kanwal SK, Shafi OM, Kumar P. Accurate estimation of body surface area in under-5 children with non-edematous severe acute malnutrition. *Journal of tropical pediatrics*. 2013;59:515-7 doi: 10.1093/tropej/fmt061.

36. Nwoye LO. Body surface area of Africans: a study based on direct measurements of Nigerian males. *Human biology*. 1989;61:439-57 [Online First: 1989/06/01].
37. van Graan CH. The determination of body surface area. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde*. 1969;43:952-9.