Downloaded from http://adc.bmj.com/ on November 9, 2015 - Published by group.bmj.com
ADC Online First, published on November 9, 2015 as 10.1136/archdischild-2015-309188

The effects of malnutrition on cardiac function in African children

Jonathan A Silverman,[1,2] Yamikani Chimalizeni,[3] Stephen E Hawes,[2] Elizabeth R Wolf,[1] Maneesh Batra,[1,2] Harriet Khofi,[3] Elizabeth M Molyneux[3]

[1]Department of Pediatrics, University of Washington School of Medicine, Seattle, Washington, USA
[2]University of Washington School of Public Health, Seattle, Washington, USA
[3]Department of Paediatrics, University of Malawi College of Medicine, Blantyre, Malawi

Correspondence to
Dr Jonathan A Silverman, Department of Emergency Medicine, Virginia Commonwealth University School of Medicine, P.O. Box 980401, Richmond, VA 23298-0401, USA; jonathan.silverman@vcuhealth.org

YC is equal first author.

Received 18 June 2015
Revised 5 October 2015
Accepted 11 October 2015

ABSTRACT

Objective Cardiac dysfunction may contribute to high mortality in severely malnourished children. Our objective was to assess the effect of malnutrition on cardiac function in hospitalised African children.

Design Prospective cross-sectional study.

Setting Public referral hospital in Blantyre, Malawi.

Patients We enrolled 272 stable, hospitalised 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, New South Wales, Australia). We used linear regression with generalised estimating equations controlling for age, sex and anaemia.

Results Our primary outcome, cardiac index, was similar between those with and without severe malnutrition: difference=0.22 L/min/m^2 (95% CI −0.08 to 0.51). 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: difference=−8.6 mm Hg (95% CI −12.7 to −4.6) and difference=−200 dyne s/cm^5/m^2 (95% CI −320 to −80), respectively.

Conclusions In this largest study to date, we found no significant difference in cardiac function between hospitalised children with and without severe acute malnutrition. Further study is needed to determine if cardiac function is diminished in unstable malnourished children.

What is known on this topic

- Children hospitalised with severe acute malnutrition have a very high mortality rate.
- The effect of severe malnutrition on cardiac function is controversial.
- Fluid management in severely malnourished children is also controversial.

What this study adds

- Cardiac index is preserved in *stable*, hospitalised children with WHO defined severe acute malnutrition.
- When children are stratified by degree of wasting, cardiac index *increases* with worsening nutritional status, commensurate with a lower systemic vascular resistance index.

BACKGROUND

Malnutrition remains a major cause of global childhood morbidity and mortality. It is estimated that malnutrition affects over 150 million children worldwide and is associated with 45% of all child deaths.[1] Malnutrition-related mortality is primarily associated with infection or dehydration, but often there is no other 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 cardiac 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] Other studies have found that cardiac function is affected pathologically in the malnourished child and decreases disproportionally 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 cardiac 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, Sydney, Australia) is a non-invasive, point of care, continuous wave Doppler ultrasound device that has been used extensively in clinical practice and validated for research,[21] though not yet employed in malnourished children. Unlike echocardiography, it is easily used by 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. An overview of these parameters with relevant formulae is provided in the appendix.

To cite: Silverman JA, Chimalizeni Y, Hawes SE, *et al*. *Arch Dis Child* Published Online First: [*please include* Day Month Year] doi:10.1136/archdischild-2015-309188

Copyright Article author (or their employer) 2015. Produced by BMJ Publishing Group Ltd (& RCPCH) under licence.

Downloaded from http://adc.bmj.com/ on November 9, 2015 - Published by group.bmj.com

The objective of our study was to assess for differences in cardiac function among stable, hospitalised children with and without severe acute malnutrition (SAM) 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 paediatric 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 or guardian prior to enrolment.

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

The study nurse performed a physical examination at the time of enrolment, documenting heart rate, respiratory rate, automated blood pressure, capillary refill time, hydration and respiratory status, oedema, and anthropometrics (weight, height, mid-upper arm circumference). Relevant clinical information such as admission diagnosis, duration of stay at time of enrolment, intravenous fluid and medication administration, HIV status (if known), and laboratory data were extracted from the patient's medical chart. We defined anaemia as haemoglobin less than 8 g/dL or haematocrit 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 haemoglobin or PCV by adding 1 g/dL or 3% for each 10 mL/kg of packed cells transfused to the pretransfusion value.

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 enrolment. 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 paediatric sphygmomanometer (Contec Medical Systems, Qinhuongdao, China).

For the primary analysis, SAM was defined according to WHO median reference values: weight for length <−3 SDs or Z scores from median; and/or mid-upper arm circumference <11.5 cm; and/or bilateral pedal oedema.[27] Our primary outcome variable was cardiac index. In our secondary analysis we categorised patients by degree of wasting: weight for length ≥−2 SD; −2 SD > weight for length ≥−3 SD; 3 SD > weight for length ≥−4 SD; or weight for length <−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% difference in cardiac index with an α of 0.05.

Statistical analysis

Our data was de-identified and collated in Excel (Microsoft, Redmond, Washington, USA) spreadsheets. We used Stata V.12.1 (College Station, Texas, USA) for analysis. We performed linear regression with generalised 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 anaemia. For our secondary analysis where wasting was stratified by Z score, we additionally controlled for the presence or absence of oedema.

This study was approved by the Malawi College of Medicine Research and Ethics Committee. 'Non-engaged' status was determined by the University of Washington independent review board (IRB).

RESULTS

We identified 272 children who met inclusion criteria (161 severely malnourished and 111 not severely malnourished) and analysed 1019 USCOM studies (median 3 studies/subject). Five children were excluded because of erroneous clinical data. The number of children screened ineligible for the study was not recorded. Baseline characteristics were similar between severely malnourished and non-severely malnourished, with the exception of HIV prevalence, which was higher among those with SAM. Duration of hospitalisation at time of enrolment was 1 day longer in the SAM group (tables 1 and 2). In our primary analysis we found that the cardiac index was similar between groups: difference=0.22 L/min/m^2 (95% CI −0.08 to 0.51) (table 3), while the cardiac output was significantly lower in those with SAM: difference=−0.34 L/min (95% CI −0.50 to −0.18) (table 4). Cardiac output, in contrast to cardiac index, does not take into account differences in BSA. 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 (table 3) and stroke volume (table 5) were significantly higher in the most wasted children. As in the primary analysis, mean arterial pressure and systemic vascular resistance index decreased with worsening

Table 1 Baseline characteristics of Malawian children aged 6–59 months, dichotomised by WHO severe acute malnutrition status

Characteristics* Median (IQR), unless otherwise specified	Not severely malnourished, n=111	Severely malnourished, n=161	p Value†
Age in months	20 (13, 33)	21 (14, 28)	0.77
Female n (%)	46 (41)	66 (41)	0.94
Hospital day at time of exam	3 (2, 3)	4 (2, 6)	<0.001
Anaemic‡ (%)	9 /87 (10)	16 /116 (14)	0.17
HIV-infected n (%)	3/76 (4)	34/126 (27)	<0.001
Mid-upper arm circumference (cm)	14.5 (13.5, 15.4)	11.8 (10.8, 13.0)	<0.001
Weight for length Z Score	−1.2 (−1.9, −0.3)	−3.3 (−4.1, −1.7)	<0.001
Length for age Z Score	−1.0 (−2.0, 0.6)	−2.8 (−3.8, −1.6)	<0.001
Marasmic n (%)	–	69 (43)	–
Marasmic kwashiorkor n (%)	–	39 (24)	–
Kwashiorkor n (%)	–	53 (33)	–

*n as per column header unless otherwise noted.
†Comparison of means derived by two-tailed t test with unequal variances.
‡Anaemia defined as haemoglobin ≤8 g/dL or packed cell volume ≤24%.

Downloaded from http://adc.bmj.com/ on November 9, 2015 - Published by group.bmj.com

Table 2 Baseline characteristics of study subjects stratified by weight for length Z score

Characteristics* Median (IQR), unless otherwise specified	Weight for length ≥−2 SD n=132	−2 SD >weight for length ≥−3 SD n=46	−3 SD >weight for length ≥−4 SD n=48	Weight for length <−4 SD n=46	p Value†
Age in months	21 (13, 33)	23 (15, 30)	18 (13, 27)	21 (17, 28)	0.57
Female n (%)	57 (43)	16 (35)	23 (48)	16 (35)	0.45
Hospital day at time of exam	3 (2, 4)	3 (2, 4)	4 (2, 6)	4 (2, 6)	0.16
Anaemic‡ n (%)	10/107 (9)	7 /36 (19)	5/30 (17)	3/30 (10)	0.02
HIV-infected n (%)	6/98 (6)	4/98 (11)	12/37 (32)	15/32 (47)	<0.01
MUAC (cm)	14 (13, 15)	13 (12, 14)	12 (11, 12)	11 (10, 11.5)	<0.01
Weight for length 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)	<0.01
Length for 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)	<0.01
Marasmic n (%)	4 (3)†	4 (9)†	33 (69)	28 (61)	<0.01
Marasmic kwashiorkor n (%)	2 (2)†	4 (9)†	15 (31)	18 (39)	<0.01
Kwashiorkor n (%)	41 (31)	12 (26)	0 (0)	0 (0)	<0.01

*n as per column header unless otherwise noted.
†Patients in this category met definition for marasmus based on MUAC.
‡Anaemia defined as haemoglobin ≤8 g/dL or packed cell volume ≤24%.
MUAC, mid-upper arm circumference.

nutritional status. However, heart rate and Smith-Madigan inotropy index were similar between the two groups.

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 difference in cardiac index. In another sensitivity analysis, we found that HIV infection had no impact on cardiac index. We observed that there was a 7.5% mortality rate in those with 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 (table 6).

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] However, one echocardiographic study of Indian children showed an *increase* in cardiac index in malnourished children compared with non-malnourished controls.[13]

When we stratified by level of wasting in our secondary analysis, we found that cardiac index was highest in the most severely wasted children (weight for length <−4 SD). Cardiac index is a function of 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. The most likely driver of the increased cardiac index in our most wasted patients was a reduced afterload. Accordingly, we found lower mean arterial pressure and systemic vascular resistance index in the 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

Table 3 Regression coefficients for cardiac index among malnourished and non-malnourished children (N=272)

	Univariable			Multivariable 1*			Multivariable 2†		
	Difference‡	95% CI	p Value	Difference‡	95% CI	p Value	Difference‡	95% CI	p Value
WHO severe malnutrition§	0.22	−0.08 to 0.52	0.14	0.22	−0.08 to 0.51	0.16	–	–	–
Malnutrition category									
Weight for length ≥−2 SD	Ref.	–	–	–	–	–	Ref.	–	–
−2 SD>Weight for length ≥−3 SD	0.18	−0.23 to 0.59	0.39	–	–	–	0.18	−0.23 to 0.59	0.38
−3 SD>Weight for length ≥−4 SD	0.28	−0.12 to 0.68	0.17	–	–	–	0.27	−0.14 to 0.68	0.20
Weight for length <−4 SD	**0.66**	**0.25 to 1.07**	**0.002**	–	–	–	**0.67**	**0.25 to 1.08**	**0.002**
Female	0.05	−0.25 to 0.35	0.75	0.05	−0.25 to 0.35	0.73	0.08	−0.22 to 0.37	0.62
Age (months)	0.00	−0.01 to 0.01	0.91	0.00	−0.01 to 0.01	0.93	0.00	−0.01 to 0.01	0.95
Oedema	−0.16	−0.33 to 0.29	0.92	–	–	–	−0.05	−0.36 to 0.26	0.78
Anaemia	0.05	−0.12 to 0.22	0.54	0.04	−0.13 to 0.21	0.61	0.01	−0.16 to 0.18	0.88

Bolded text is for parameters with p-values <0.05.
*Adjusted for age, sex, anaemia with exposure of interest being WHO severe malnutrition.
†Adjusted for age, sex, anaemia and oedema with exposure of interest being wasting (malnutrition), stratified by Z-score or SD.
‡Coefficients derived using generalised estimation equations with exchangeable correlation matrices.
§Weight for length <−3 SD and/or mid-upper arm circumference (MUAC) <11.5 and/or oedema.

Downloaded from http://adc.bmj.com/ on November 9, 2015 - Published by group.bmj.com

Table 4 Difference in multivariable adjusted cardiac parameters (95% CI) among 272 children dichotomised 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, n=111	ref	ref	ref	ref	ref	ref
WHO severe acute malnutrition present, n=161	**−0.34 (−0.50 to -0.18)**	−0.11 (−0.23 to 0.01)	0.89 (−1.43 to 3.21)	0.04 (−3.93 to 4.00)	**−8.62 (−12.67 to −4.58)**	**−200 (−320 to −80)**

*Adjusted for age, sex, and anaemia status.

Table 5 Difference in multivariable adjusted cardiac parameters (95% CI) among 272 malnourished and non-malnourished children stratified by Z score*

	Cardiac output (L/min)	Smith-Madigan inotropy index (W/m^2)	Stroke volume index (mL/beat/m^2)	Heart rate (beats/min)	Mean arterial pressure (mm Hg)	Systemic vascular resistance index (dyne s/cm^5/m^2)
Weight for length ≥−2 SD, n=132	ref	ref	ref	ref	ref	ref
−2 SD > Weight for length ≥−3 SD, n=46	−0.13, (−0.35 to 0.08)	−0.08 (−0.24 to 0.08)	2.84 (−0.31 to 5.99)	0.90 (−4.58 to 6.38)	**−6.78 (−12.37 to −1.18)**	**−197 (−360 to −34)**
−3 SD > Weight for length ≥−4 SD, n=48	**−0.30, (−0.54 to −0.07)**	−0.01 (−0.17 to 0.16)	1.78 (−1.37 to 4.94)	2.27 (−3.21 to 7.74)	−5.19 (−10.77 to 0.40)	**−191 (−355 to −28)**
Weight for length <−4 SD, n=46	**−0.32 (−0.55 to −0.08)**	0.09 (−0.08 to 0.26)	**5.62 (2.43 to 8.80)**	2.94 (−2.58 to 8.46)	**−11.02 (−16.65 to −5.40)**	**−346 (−511 to −181)**

*Adjusted for age, sex, anaemia status and oedema.
Numbers in bold are statistically significant, ie p<0.05.

Table 6 Results of sensitivity analyses for cardiac index among malnourished and non-malnourished children (N=272)

	Primary analysis*			Sensitivity analysis 1†			Sensitivity analysis 2‡			Sensitivity analysis 3*§		
	Difference‡	95% CI	p Value	Difference‡	95% CI	p Value	Difference‡	95% CI	p Value	Difference‡	95% CI	p Value
WHO severe malnutrition§	0.22	−0.08 to 0.51	0.16	0.20	−0.11 to 0.52	0.21	0.27	−0.06 to 0.60	0.11	0.24	−0.23 to 0.37	0.64

*Multivariable analysis adjusted for age, sex and anaemia status.
†Multivariable analysis adjusted for age, sex, anaemia status and hospital day (n=270).
‡Multivariable analysis adjusted for age, sex, anaemia status and known HIV infection.
§Analysis excluded 14 children who died (n=12) or whose status at discharge was not recorded (n=2).

Downloaded from http://adc.bmj.com/ on November 9, 2015 - Published by group.bmj.com

normalised by body weight increased quickly with oral and intravenous 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 we included day of hospitalisation and refeeding prior to examination in the model. It should also be noted that our findings are not consistent with classical 'refeeding syndrome', whereby fluid and electrolyte shifts are associated with cardiac failure upon refeeding, with patients exhibiting tachycardia, increased systemic vascular resistance and decreased stroke volume.[30] Such patients would have likely been excluded from our study due to their haemodynamic instability.

In contrast to the increased cardiac function observed in nutritional recovery, other studies observed worse systolic function in the acutely malnourished.[16 17] Of note, one study in Zaire using pulmonary artery catheterisations 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. By excluding children who were clinically unstable, we are unable to generalise our findings to acutely ill malnourished children. Further studies will be necessary to investigate heart function in decompensated children with severe malnutrition.

Furthermore, obtaining USCOM measurements on small and often uncooperative children was technically challenging. However, since the same nurse performed the studies in both comparison groups, it is unlikely that this would have affected the results. Another technical limitation to our study is that we used weight at time of examination to categorise 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 oedema 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 when stratified by severity of wasting.

It is also possible that the nomogram that estimates aortic outflow tract diameter used by the USCOM software, based on height,[31] overestimates or underestimates this parameter in the malnourished. However, the investigators who derived the nomogram found that adding BSA or weight to the model did not improve accuracy over height alone. It is reassuring that the presence of wasting should not limit the application of the nomogram in 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 with echocardiography and pulmonary artery catheterisation.[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 affect the validity of our findings.

We excluded unstable children to minimise 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, we still found no differences between the groups (table 6).

We used cardiac index (cardiac output normalised by BSA) to compare groups since BSA is often used as a marker for metabolic demand. However, it is unclear how well 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 questions may be whether these children have adequate cardiac function for their needs, which may be adaptively minimised in the malnourished state, and whether their hearts could withstand an acute physiological stressor.

Conclusion

In summary, we did not observe significant differences in cardiac index of stable hospitalised Malawian children with and without SAM. However, the subset of most severely wasted children (weight for length <−4 SD) demonstrated higher mean cardiac index, likely as a result of decreased afterload. Future studies are needed to better understand heart function and guide resuscitation in critically ill malnourished children.

Contributors JAS and YC contributed equally to the overall project. JAS and EMM conceived of the project. JAS, EMM and YC designed the study. HK, YC and EMM performed and supervised data collection. Data analysis and manuscript preparation was led by JAS, SEH, ERW and MB. All authors were involved in revision of the manuscript.

Funding The study received $2500 of unallocated research funds from the paediatric department of the Queen Elizabeth Central Hospital.

Competing interests None declared.

Ethics approval Malawi College of Medicine Research and Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Unpublished data on baseline characteristics and USCOM cardiovascular parameters are available from the corresponding author.

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.
2 Smythe PM, Swanepoel A, Campbell JA. The heart in kwashiorkor. *BMJ* 1962;1:67–73.
3 Brewster DR. Critical appraisal of the management of severe malnutrition: 3. Complications. *J Paediatr Child Health* 2006;42:583–93.
4 World Health Organization. *Management of severe malnutrition: a manual for physicians and other senior health workers*. WHO. Geneva, 1999.
5 Akech SO, Karisa J, Nakamya P, *et al*. Phase II trial of isotonic fluid resuscitation in Kenyan children with severe malnutrition and hypovolaemia. *BMC Pediatr* 2010;10:71.
6 Webb JG, Kiess MC, Chan-Yan CC. Malnutrition and the heart. *CMAJ* 1986;135:753–8.
7 El-Sayed HL, Nassar MF, Habib NM, *et al*. Structural and functional affection of the heart in protein energy malnutrition patients on admission and after nutritional recovery. *Eur J Clin Nutr* 2006;60:502–10.
8 Bergman JW, Human DG, De Moor MM, *et al*. Effect of kwashiorkor on the cardiovascular system. *Arch Dis Child* 1988;63:1359–62.
9 Singh GR, Malathi KE, Kasliwal RR, *et al*. An evaluation of cardiac function in malnourished children by non-invasive methods. *Indian Pediatr* 1989;26:875–81.
10 Shoukry I, Shoukry A, Ibrahim MM, *et al*. Cardiac atrophy and ventricular function in infants with severe protein calorie malnutrition (Kwashiorkor Disease). In: Doyle E,

Downloaded from http://adc.bmj.com/ on November 9, 2015 - Published by group.bmj.com

Engle M, Gersony W, Rashkind W, Talner N, eds. *Pediatric cardiology*. New York: Springer, 1986:1169–71.
11 Olivares JL, Vázquez M, Rodríguez G, *et al*. Electrocardiographic and echocardiographic findings in malnourished children. *J Am Coll Nutr* 2005;24:38–43.
12 Ocal B, Unal S, Zorlu P, *et al*. Echocardiographic evaluation of cardiac functions and left ventricular mass in children with malnutrition. *J Paediatr Child Health* 2001;37:14–17.
13 Kothari SS, Patel TM, Shetalwad AN, *et al*. Left ventricular mass and function in children with severe protein energy malnutrition. *Int J Cardiol* 1992;35:19–25.
14 Viart P. Hemodynamic findings in servere protein-calorie malnutrition. *Am J Clin Nutr* 1977;30:334–48.
15 Viart P. Hemodynamic findings during treatment of protein-calorie malnutrition. *Am J Clin Nutr* 1978;31:911–26.
16 Olowonyo MT, Akinbami FO, Ogunkunle OO, *et al*. The electrocardiographic changes in kwashiorkor. *Ann Trop Paediatr* 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. *Am J Physiol* 1947;150:153–69.
18 Alleyne GA. Cardiac function in severely malnourished Jamaican children. *Clin Sci* 1966;30:553–62.
19 Phornphatkul C, Pongprot Y, Suskind R, *et al*. Cardiac function in malnourished children. *Clin Pediatr (Phila)* 1994;33:147–54.
20 Otieno H, Were E, Ahmed I, *et al*. Are bedside features of shock reproducible between different observers? *Arch Dis Child* 2004;89:977–9.
21 Cattermole GN, Leung PY, Mak PS, *et al*. The normal ranges of cardiovascular parameters in children measured using the Ultrasonic Cardiac Output Monitor. *Crit Care Med* 2010;38:1875–81.
22 Dey I, Sprivulis P. Emergency physicians can reliably assess emergency department patient cardiac output using the USCOM continuous wave Doppler cardiac output monitor. *Emerg Med Australas* 2005;17:193–9.
23 Corley A, Barnett AG, Mullany D, *et al*. Nurse-determined assessment of cardiac output. Comparing a non-invasive cardiac output device and pulmonary artery catheter: a prospective observational study. *Int J Nurs Stud* 2009;46:1291–7.
24 Wongsirimetheekul T, Khositseth A, Lertbunrian R. Non-invasive cardiac output assessment in critically ill paediatric patients. *Acta Cardiol* 2014;69:167–73.
25 Krovetz LJ. The physiologic significance of body surface area. *J Pediatr* 1965;67:841–62.
26 Smith BE, Madigan VM. Non-invasive method for rapid bedside estimation of inotropy: theory and preliminary clinical validation. *Br J Anaesth* 2013;111:580–8.
27 World Health Organization. *Guideline: updates on the management of severe acute malnutrition in infants and children*. WHO. Geneva, 2013.
28 Heymsfield SB, Bethel RA, Ansley JD, *et al*. Cardiac abnormalities in cachectic patients before and during nutritional repletion. *Am Heart J* 1978;95:584–94.
29 Heymsfield SB, Head CA, McManus CB III, *et al*. Respiratory, cardiovascular, and metabolic effects of enteral hyperalimentation: influence of formula dose and composition. *Am J Clin Nutr* 1984;40:116–30.
30 Fuentebella J, Kerner JA. Refeeding syndrome. *Pediatr Clin North Am* 2009;56:1201–10.
31 Nidorf SM, Picard MH, Triulzi MO, *et al*. New perspectives in the assessment of cardiac chamber dimensions during development and adulthood. *J Am Coll Cardiol* 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. *Br J Anaesth* 2009;103:800–4.
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.
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, *et al*. Accurate estimation of body surface area in under-5 children with non-edematous severe acute malnutrition. *J Trop Pediatr* 2013;59:515–17.
36 Nwoye LO. Body surface area of Africans: a study based on direct measurements of Nigerian males. *Hum Biol* 1989;61:439–57.
37 van Graan CH. The determination of body surface area. *S Afr Med J* 1969;43:952–9.

Appendix: Cardiovascular indices

The stroke volume is the amount of 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×heart rate. Dividing the cardiac output by the BSA, one obtains the cardiac index, which standardises 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, standardised 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 versus high systemic vascular resistance states[26] but still requires further validation.
Cardiovascular indices:

$$\text{Cardiac Output} = \text{Heart Rate} \times \text{Stroke Volume}$$
$$\text{Cardiac Index} = \text{Cardiac Output/Body Surface Area}$$
$$\text{Systemic Vascular Resistance Index} = \text{Mean Arterial Pressure/Cardiac Index}$$
$$\text{Smith Madigan Inotropy Index} = (\text{Bpmean} \times \text{Svol} \times 10^{-3})/(7.5 \times \text{FT}) + (\text{Svol} \times 10^{-6} \times \rho\text{Vmean}^2)/2 \times \text{FT}$$

where Bpmean, mean arterial pressure—central venous pressure in mm Hg; Svol, stroke volume in mL; Vmean, mean velocity in m/s; FT, flow time in milliseconds, and ρ, blood density in kg/m^3.[26]

Downloaded from http://adc.bmj.com/ on November 9, 2015 - Published by group.bmj.com

The effects of malnutrition on cardiac function in African children

Jonathan A Silverman, Yamikani Chimalizeni, Stephen E Hawes, Elizabeth R Wolf, Maneesh Batra, Harriet Khofi and Elizabeth M Molyneux

Arch Dis Child published online November 9, 2015

Updated information and services can be found at:
http://adc.bmj.com/content/early/2015/11/08/archdischild-2015-309188

These include:

References This article cites 34 articles, 11 of which you can access for free at:
http://adc.bmj.com/content/early/2015/11/08/archdischild-2015-309188#BIBL

Email alerting service Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections Articles on similar topics can be found in the following collections

Hypertension (360)
Stroke (224)
Epidemiologic studies (1738)
Clinical diagnostic tests (1094)
Radiology (943)
Radiology (diagnostics) (742)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/