

Acute Malnutrition and Hypertension

Impaired Cardiovascular Structure and Function in Adult Survivors of Severe Acute Malnutrition

Ingrid A. Tennant, Alan T. Barnett, Debbie S. Thompson, Jan Kips, Michael S. Boyne, Edward E. Chung, Andrene P. Chung, Clive Osmond, Mark A. Hanson, Peter D. Gluckman, Patrick Segers, J. Kennedy Cruickshank,* Terrence E. Forrester*

Abstract—Malnutrition below 5 years remains a global health issue. Severe acute malnutrition (SAM) presents in childhood as oedematous (kwashiorkor) or nonoedematous (marasmic) forms, with unknown long-term cardiovascular consequences. We hypothesized that cardiovascular structure and function would be poorer in SAM survivors than unexposed controls. We studied 116 adult SAM survivors, 54 after marasmus, 62 kwashiorkor, and 45 age/sex/body mass index–matched community controls who had standardized anthropometry, blood pressure, echocardiography, and arterial tonometry performed. Left ventricular indices and outflow tract diameter, carotid parameters, and pulse wave velocity were measured, with systemic vascular resistance calculated. All were expressed as SD scores. Mean (SD) age was 28.8±7.8 years (55% men). Adjusting for age, sex, height, and weight, SAM survivors had mean (SE) reductions for left ventricular outflow tract diameter of 0.67 (0.16; $P<0.001$), stroke volume 0.44 (0.17; $P=0.009$), cardiac output 0.5 (0.16; $P=0.001$), and pulse wave velocity 0.32 (0.15; $P=0.03$) compared with controls but higher diastolic blood pressures (by 4.3; 1.2–7.3 mmHg; $P=0.007$). Systemic vascular resistance was higher in marasmus and kwashiorkor survivors (30.2 [1.2] and 30.8 [1.1], respectively) than controls 25.3 (0.8), overall difference 5.5 (95% confidence interval, 2.8–8.4 mmHg min/L; $P<0.0001$). No evidence of large vessel or cardiac remodeling was found, except closer relationships between these indices in former marasmic survivors. Other parameters did not differ between SAM survivor groups. We conclude that adult SAM survivors had smaller outflow tracts and cardiac output when compared with controls, yet markedly elevated peripheral resistance. Malnutrition survivors are thus likely to develop excess hypertension in later life, especially when exposed to obesity. (*Hypertension*. 2014;64:664–671.) • [Online Data Supplement](#)

Key Words: blood supply ■ kwashiorkor ■ protein-energy malnutrition

Malnutrition contributes significantly to global mortality among children aged <5 years.^{1,2} Undernutrition before and during pregnancy alters development, increasing offspring risk of obesity and cardiovascular disease.³ Undernutrition in infancy while offspring remain developmentally plastic also increases the risk of cardiovascular disease in adulthood.^{2,4,5}

Little is currently known about the effect of childhood malnutrition on adult risk of cardiovascular disease. Pooled analyses on participants undernourished in early childhood from low- and middle-income countries showed that weight, height, and body mass index at age 2 years had strong negative relationships with adult systolic blood pressure, even adjusting for weight.⁶ Dutch adults, exposed to famine as children or adolescents, had an excess coronary events, but lower stroke rates.⁷ Rates of type 2 diabetes mellitus were 25% higher in

those moderately exposed to the famine and 50% in those severely exposed.⁸ Similar but larger risks were recorded for prenatal exposure to the acute malnutrition during pregnancy in that famine; a 4-fold excess cardiovascular mortality occurred in female offspring exposed in utero to famine in early gestation.⁹

Damage to cardiovascular structure or function arising from severe acute malnutrition (SAM) would have global public health significance. The damage could also differ between the 2 SAM syndromes: kwashiorkor and marasmus. We have used a retrospective cohort of adult survivors of SAM previously treated in the Tropical Metabolism Research Unit, Kingston, Jamaica, to explore the effects of malnutrition on adult cardiovascular structure and function and shown that birth weight is 333 g lower in infants presenting with marasmus when

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From the Tropical Medicine Research Institute (D.S.T., M.S.B.), Departments of Surgery, Radiology, Anaesthesia, and Intensive Care (I.A.T., A.T.B.), Medicine (Cardiology) (E.E.C., A.P.C.), and UWI Solutions for Developing Countries (T.E.F.), University of the West Indies, Mona, Kingston, Jamaica; Institute Biomedical Technology, Ghent University, Ghent, Belgium (J.K., P.S.); MRC Lifecourse Epidemiology Unit (C.O.) and DOHAD Division (M.A.H.), University of Southampton, Southampton, United Kingdom; Centre for Human Evolution, Adaptation, and Disease, Liggins Institute, University of Auckland, Auckland, New Zealand (P.D.G.); and Division of Diabetes, Cardiovascular Medicine, and Nutrition, King's College and King's Health Partners, London, United Kingdom (J.K.C.).

*These authors are joint last authors.

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Correspondence to Terrence E. Forrester, UWI Solutions for Developing Countries, 25 West Rd, University of the West Indies, Mona, Kingston, Jamaica. E-mail terrence.forrester@uwimona.edu.jm

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compared with those with kwashiorkor.¹⁰ Lower birth weight suggests more severe intrauterine undernutrition, and marasmus survivors would, therefore, be expected to have greater later cardiovascular dysfunction than after kwashiorkor. However, because children with kwashiorkor are less able to sustain amino acid and lipid supply than children with marasmus,^{11,12} kwashiorkor children may also have poorer cardiovascular development, with later consequences for risk.

We hypothesized that SAM survivors aged ≈ 30 years would have impaired cardiovascular structure and function when compared with controls unexposed to SAM, and that there could be differences in cardiovascular measures between kwashiorkor and marasmus survivors. To test our hypotheses, we measured arterial stiffness (pulse wave velocity [PWV]), left ventricular (LV) mass, other LV and carotid artery indices, and body composition.

Methods

Study Design/Subjects

We sampled subjects from all 1336 adults who had been admitted as children to the Metabolic Ward of Tropical Metabolism Research Unit during 1963 to 1993. Average age at original admission was 11.6 months (marasmic group) and 12.4 months (kwashiorkor).¹⁰ Tropical Metabolism Research Unit has treated SAM since 1956, using standardized feeding protocols, and mortality rates approximate 4%.^{10,13} A total of 629 subjects were traced as adults by community health aides and nurses. Of these, 28 had died (cause of death unknown), 140 were not found at their last known address, and 94 did not participate because of migration (n=53), mental incompetence (n=16), pregnancy (n=3), missing hospital records (n=6), or were unavailable (n=16). A total of 116 of the remaining 367 consented to have cardiovascular assessments. Admission data (age, weight, height, and presence of edema) were extracted from hospital records. Malnutrition was classified using Wellcome criteria.¹⁴ Those with moderate wasting (weight for age between 60th and 80th centile) and edema had kwashiorkor; and those with severe wasting (weight for age <60th centile) and edema had marasmic-kwashiorkor; and those with severe wasting without edema had marasmus. For analysis, we combined the kwashiorkor and marasmic-kwashiorkor subjects into an oedematous group, and the marasmus subjects formed the nonoedematous group.

Community controls who had never experienced SAM were also recruited. Recruiters went from house to house alternately on either side of the index case's address and identified patients matched by age (within 5 years), sex, and body mass index (within 2 kg/m²) who were willing to participate. On average, 10 patients were screened to identify a control for each SAM survivor. Within the staffing time available, 45 (39%) controls were studied.

The Faculty of Medical Sciences, University Hospital of the West Indies Ethics Committee approved the study protocol. All participants gave written informed consent.

Cardiovascular Measurements

All participants fasted overnight before measurements with no strenuous exercise, alcohol, and caffeine for the preceding 12 hours. Participants with acute illnesses were excluded. Height and weight were measured in light clothing, to calculate body mass index (kg/m²). Participants rested for >10 minutes supine in a temperature-controlled environment (22 \pm 1°C). Supine blood pressures were recorded in triplicate on the right arm, 2 minutes apart using an Omron HEM790IT sphygmomanometer. The last 2 measurements were averaged for analysis. Mid-upper arm circumference guided selection of appropriate sized sphygmomanometer cuffs.

Augmentation index, the difference between second and first systolic peaks as a percentage of pulse pressure, was derived from applanation tonometry¹⁵ using a Millar pen-type tonometer and National Instruments SC-2345 signal acquisition and conditioning hardware.

A graphical user interface in Matlab (Mathworks, Natick, MA) was used to acquire and process the data. Tonometry was performed at the right brachial artery, with quality checks to ensure stable waveforms, then at the right radial and right carotid arteries.

Vascular ultrasound was performed using a GE Vivid *i* ultrasound machine (Fairfield, CT) with a vascular 8 L probe. Participants were recumbent with the neck in slight hyperextension, tilted $\approx 30^\circ$ to the left. The right carotid and femoral arteries were imaged and intima-medial thickness (IMT) measured, 1 to 2 cm proximal to the carotid bulb or femoral bifurcation. Measurements were made on the posterior wall using electronic calipers, with the ECG triggered on the R-wave. Three measurements were taken, and the average was analyzed. Similarly, the right carotid end-diastolic wall and lumen diameters were measured, and derived cross-sectional surface areas were estimated (Tables 1–4), also expressed together with IMT.

Doppler methods for measuring PWV have good reproducibility, as established in original work ≥ 25 year ago¹⁶ and prognostically.¹⁷ As in the Asklepios Study, PWV was measured from ECG-gated Doppler flow waveforms (using the GE Vivid *i* machine described above), 1 to 2 cm proximal to the carotid bulb and femoral bifurcation.^{18,19}

PWV was calculated as $\Delta L/\Delta t$, with ΔL 80% of the direct distance between carotid and femoral location²⁰ and Δt , transit time, the time delay between the feet of the 2 waveforms. Arterial tonometry and vascular ultrasound were conducted by 3 researchers, with good repeatability (within and between observer variation <6%). One of the researchers (J.K.) was from the Asklepios study and did 40% of these measures and trained the other 2 researchers.

Two-dimensional, M-mode and Doppler transthoracic echocardiography, also using the GE vivid, was performed with a cardiac 3S probe, in the left lateral recumbent position, obtaining standard parasternal short- and long-axis, apical, subcostal, and suprasternal views. All measurements were ECG gated with sweep speed set at 100 mm/s. Images and loops were exported in digital imaging and communications in medicine format. Stroke volume, LV mass, and outflow tract internal diameter were measured by 2 cardiologists when compared against each other extensively throughout the study, with blinded off-line reading. Cardiac output (CO) was derived using standard techniques, as was systemic vascular resistance (SVR) as mean arterial pressure=(2/3 diastolic+1/3 systolic)/CO.

CT Measurements

We used 1 cross-sectional scan at the L4-5 interspace on a Phillips Brilliance 64-slice scanner (Amsterdam, The Netherlands). Subjects were examined supine with arms outstretched overhead using the following parameters: 120 kV, 100-mA exposure, and 5-mm slice thickness. Total and intra-abdominal (visceral) fat mass and area were measured using the QCT Pro software.

Statistical Methods

Cardiovascular measures were right-skewed, so we used a Fisher-Yates transformation, separately by sex, to normalize and standardize the variables. We used multiple linear regression analysis to assess differences in these standardized measures, between all survivors combined and controls, and then between nonoedematous and oedematous survivors. We first included age and sex, then added height and weight. We used SPSS version 19 (IBM, Chicago, IL), with $P < 0.05$.

Results

The 161 participants' mean age was 28.8 \pm 7.8 years; 88 (55%) were men; 54 (34%) were nonoedematous; 62 oedematous (38%) SAM survivors; and 45 (28%) controls (Table 1). The 116 survivors of SAM in this study did not differ in their anthropometric indices from the 1220 subjects not recruited. There were similar proportions of men and women, patients with kwashiorkor and marasmus, as well as no differences in birth weight, age, and height for age at admission between those studied and those not recruited.

Table 1. Clinical Characteristics of 116 Survivors of Childhood SAM and 45 Community Controls, According to Sex

Measurement Mean (SD)	SAM Phenotype		
	Nonoedematous	Oedematous	Control
Men			
n	29	41	18
Age, y	29.2 (8.4)	27.2 (7.8)	29.7 (5.1)
Height, cm	170.5 (7.7)	172.2 (7.7)	174.1 (5.6)
Weight, kg	62.3 (13.4)	67.3 (10.1)	68.7 (10.6)
Body mass index, kg/m ²	21.3 (3.6)	22.7 (3.0)	22.7 (3.5)
Visceral fat mass, g*	10.4 (7.3, 20.1)	9.1 (8.1, 15.3)	11.5 (5.2, 26.6)
Systolic blood pressure, mm Hg	118.9 (14.7)	118.6 (9.5)	118.5 (11.7)
Diastolic blood pressure, mm Hg	73.1 (9.4)	72.3 (7.1)	70.6 (9.7)
Heart rate, bpm	55.5 (9.0)	53.5 (8.5)	54.6 (6.4)
Secondary education, %	71	63	63
Monthly income >US\$186, %	64	57	43
Women			
n	25	21	27
Age, y	28.3 (7.6)	30.4 (9.1)	29.4 (8.3)
Height, cm	160.9 (7.5)	161.5 (8.2)	161.7 (6.0)
Weight, kg	63.5 (19.1)	69.5 (17.4)	68.0 (18.0)
Body mass index, kg/m ²	24.4 (6.7)	26.7 (6.9)	26.0 (6.7)
Visceral fat mass, g*	23.5 (12.4, 30.2)	20.2 (17.3, 37.5)	20.5 (15.4, 35.5)
Systolic blood pressure, mm Hg	111.7 (12.8)	116.4 (17.7)	110.7 (18.67)
Diastolic blood pressure, mm Hg	74.2 (11.7)	77.8 (12.7)	71.2 (9.5)
Heart rate, bpm	66.5 (10.4)	61.3 (9.1)	65.9 (7.5)
Secondary education, %	75	90	88
Monthly income >US\$186, %	32	35	61

SAM indicates severe acute malnutrition.

*Median (lower quartile, upper quartile).

Patients with kwashiorkor had slightly greater weight for age (measured weight/expected weight as a percentage) at admission (60.0 ± 9.8 versus 57.7 ± 10.8 ; $P=0.06$) and in weight for height (68.3 ± 9.0 versus 66.1 ± 10.0 ; $P=0.05$). We also compared the 116 subjects who underwent cardiovascular studies with the remaining 196 subjects recruited, who had anthropometric but no cardiovascular measurements. There were no significant differences between these groups in age ($P=0.2$), sex ($P=0.9$), body mass index ($P=0.5$), or visceral fat mass ($P=0.5$).

There was no difference in weight or visceral fat mass between SAM survivors and controls. Baseline measures of systolic blood pressure and heart rate were normal and not significantly different between groups (Table 1). However, diastolic blood pressure was significantly increased in both oedematous and nonoedematous SAM survivors when compared with controls (4.3 mmHg; 95% confidence interval, 1.2–7.3 mmHg; $P=0.007$). There were no significant sex-related cardiovascular findings, but by malnutrition group (Table 2), major differences emerged between all former SAM cases and controls (Table 3). Controls had greater left ventricular outflow tract (LVOT) diameter, stroke volume, CO, and femoral IMT than SAM survivors. Their ejection fraction was lower but PWV was higher than SAM survivors. There

were no differences in carotid IMT, IMT:carotid luminal or wall diameter, or other wall:lumen ratios, LV mass, or augmentation index. Further controlling for visceral fat mass had little effect (data not shown). These measures were not significantly different between oedematous and nonoedematous SAM survivors, except heart rate, after controlling for age, sex, height, and weight.

A striking finding was a higher SVR in SAM survivors, 5.5 (95% confidence interval, 2.8–8.4) mmHg min/L than controls. That result was primarily related to lower CO at similar systolic, but at higher diastolic, pressures; hence, marginally higher mean pressures were observed. There was a marked inverse correlation between LVOT diameter and SVR (Figure 1; $r=-0.57$; $P<0.0001$). A correlation between SVR and larger vessel PWV ($r=-0.1$) was weaker and not significant.

If body surface area rather than height and weight were used for adjustment, differences in results were minimal and none of those above were altered, except for PWV. Therefore, if using the Dubois formula (body surface area= W (kg)^{0.425} $\times H$ (cm)^{0.725} $\times 0.007184$), the result was the same (PWV SD difference [Table 3] was 0.32; $P=0.03$); if body surface area was approximated by height^{1.7} (as for Europeans²¹), then that SD difference was 0.26, no longer significant ($P=0.77$).

Table 2. Cardiovascular Measures by Childhood Nutritional Diagnosis During SAM

Measurement	Mean (SD)		
	SAM Phenotype		
	Nonoedematous	Oedematous	Control
n	54	62	45
cIMT, mm	0.51 (0.09)	0.51 (0.09)	0.53 (0.08)
Carotid CSA, mm ²	1.70 (0.48)	1.71 (0.47)	1.78 (0.43)
cIMT/CSA ratio	0.3 (0.03)	0.3 (0.03)	0.3 (0.03)
cLdD, mm	5.4 (0.5)	5.5 (0.6)	5.4 (0.5)
cWD/cLdD ratio	2.7 (0.3)	2.7 (0.4)	2.8 (0.4)
Femoral IMT, mm	0.47 (0.09)	0.47 (0.10)	0.52 (0.08)
Pulse wave velocity, m/s	5.7 (1.1)	5.6 (1.6)	6.1 (1.2)
Stroke volume, mL	54.1 (14.8)	57.2 (15.8)	59.9 (13.2)
Cardiac output, L/min	3.2 (0.8)	3.2 (0.8)	3.6 (0.8)
Systemic vasc resist, mm Hg*min/L	30.2 (8.5)	30.8 (8.3)	25.3 (5.4)
Ejection fraction, %	65.1 (8.1)	64.3 (8.3)	62.8 (7.7)
Augmentation index, %	103.5 (17.8)	105.4 (44.9)	100.3 (14.9)
LV mass index, g/m ²	48.6 (15.2)	53.4 (16.1)	48.9 (12.0)
LV outflow tract diameter, cm	2.0 (0.2)	2.0 (0.2)	2.2 (0.2)
LVEDV	92.7 (23.7)	102.1 (33.7)	91.3 (21.5)
M/V ratio	1.47 (0.27)	1.46 (0.19)	1.50 (0.19)
Central SBP, mm Hg	112.7 (16.5)	114.2 (14.0)	111.5 (19.3)

CSA indicates cross-sectional area; cIMT, carotid intima-medial thickness; cWD/cLdD, carotid wall diameters/carotid lumen diameters in diastole; IMT, intima-medial thickness; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; M/V, mass:volume; SAM, severe acute malnutrition; and SBP, systolic blood pressure.

Relationships Between Cardiac Geometry and Arterial Parameters

We examined large artery structure for remodeling and then its relationship with LV remodeling, testing carotid wall diastolic cross-sectional area, carotid wall diameters, lumen diameters in diastole, and their ratios (Tables 2 and 3). Carotid wall diastolic cross-sectional area was no different between SAM subgroups, but again, like the LVOT, tended to be smaller adjusted for age and sex in all former cases than in controls (0.28 SD; $P=0.09$; Table 3). Further adjustment for height and weight had little effect ($P=0.1$).

Indices of LV remodeling included LV mass indexed to body size, LV end-diastolic volume, a volume-sensitive parameter, and the more pressure-sensitive mass:volume ratio. Again there were no major differences between former cases or between all former cases and controls in absolute values (which, despite the slight increase in diastolic BP, were somewhat less than in patients with hypertension).^{22,23}

However, intriguingly, relationships between cardiac and large artery (carotid) parameters were related to case status; unadjusted, the slopes between LV mass indexed and carotid WSA for former cases (Figure 2A) or controls (Figure 2B) were similar. However, after adjustment for age, sex, height, and weight, the relationships were stronger and highly significant in former cases (adjusted $r=0.3-0.5$) but not in controls (0.1), possibly also for LV end-diastolic volume, but confined to former marasmic cases for mass:volume ratio (Table 4).

There were no significant relationships between evidence of wasting (weight for height) or stunting (height for age) at

admission in childhood and any adult cardiovascular measurement. We did not have follow-up anthropometric measurements on these children until this follow-up and so any relationships between cardiovascular structure and function and catch-up growth during childhood or adolescence are unknown.

Discussion

To our knowledge, this is the first report of abnormal cardiovascular structure and function in survivors of SAM. These findings are relevant to large numbers of people previously exposed to malnutrition across the world. Such effects could originate in utero,^{24,25} but may also result from, or be exacerbated by, the malnutrition insult in early childhood.

Comparison of Survivors and Controls

Adult survivors of severe childhood malnutrition had smaller LVOT diameters and decreased stroke volume, CO, and higher SVR than controls. The degree of difference is considerable, approximately half a SD between SAM survivors and controls.

LVOT Diameter, SV, and CO

The decrease in LVOT diameter, stroke volume, and CO in SAM survivors when compared with controls might reflect a combination of pre- and postnatal insults because nutritional insults in both these developmentally plastic periods can limit organ development. Fetal redistribution of blood flow to preserve brain development mediates other organ underdevelopment.^{26,27} Animal studies suggest that adult cardiomyocyte

Table 3. Differences in Cardiovascular Measures (SD scores) for Survivors of SAM in Oedematous Versus Nonoedematous Forms and Between Controls Versus All SAM Survivors

Measurement (Standardized Score)	Oedematous–Nonoedematous			Controls–All SAM Survivors		
	Difference	95% CI	P Value	Difference	95% CI	P Value
Controlled for age, sex, height, and weight						
Visceral fat mass	−0.28	−0.64 to 0.09	0.1	−0.07	−0.38 to 0.24	0.6
Systolic blood pressure	−0.05	−0.38 to 0.28	0.8	−0.28	−0.59 to 0.04	0.08
Diastolic blood pressure	−0.02	−0.35 to 0.31	0.9	−0.43	−0.73 to −0.12	0.007
Heart rate	−0.45	−0.84 to −0.05	0.03	0.23	−0.12 to 0.59	0.2
cIMT	−0.05	−0.43 to 0.32	0.8	0.25	−0.08 to 0.58	0.1
Carotid CSA	−0.03	−0.40 to 0.34	0.9	0.25	−0.08 to 0.57	0.1
cIMT/cCSA ratio	0.003	−0.36 to 0.36	1.0	−0.19	−0.51 to 0.14	0.3
cLdD	0.05	−0.3 to 0.41	0.8	0.04	−0.30 to 0.37	0.8
cWD (calc) to cLdD ratio	−0.1	−0.47 to 0.28	0.6	0.18	−0.17 to 0.52	0.3
Femoral IMT	−0.06	−0.41 to 0.30	0.8	0.71	0.34 to 1.08	<0.001
Pulse wave velocity*	−0.09	−0.05 to 0.17	0.6	0.32	0.02 to 0.61	0.04
Stroke volume	0.07	−0.31 to 0.44	0.7	0.44	0.11 to 0.77	0.009
Cardiac output	−0.20	−0.55 to 0.15	0.3	0.53	0.21 to 0.85	0.001
Systemic vascular resistance	0.20	−0.17 to 0.57	0.3	−0.67	−1.01 to −0.33	<0.001
Ejection fraction	−0.06	−0.45 to 0.34	0.8	−0.42	−0.77 to −0.07	0.02
Augmentation Index	−0.04	−0.38 to 0.31	0.8	−0.19	−0.50 to 0.11	0.2
LV mass index	0.17	−0.17 to 0.52	0.3	−0.03	−0.33 to 0.28	0.9
LV outflow tract diameter	−0.17	−0.51 to 0.18	0.3	0.67	0.36 to 0.99	<0.001
LVEDV	0.11	−0.26 to 0.47	0.6	−0.09	−0.43 to 0.25	0.6
M/V ratio	0.06	−0.34 to 0.47	0.8	−0.04	−0.41 to 0.33	0.8
Central systolic BP	−0.04	−0.38 to 0.30	0.8	−0.20	−0.51 to 0.11	0.2

BP indicates blood pressure; cCSA, carotid cross-sectional area; CI, confidence interval; cIMT, carotid intima-medial thickness; cWD/cLdD, carotid wall diameters/carotid lumen diameters in diastole; IMT, intima-medial thickness; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; M/V, mass:volume; and SAM, severe acute malnutrition.

*Additionally adjusted for diastolic blood pressure and heart rate.

numbers are set prenatally, and that stressors during this period can lead to decreased cell numbers that persist into adult life.²⁴ Our results are thus compatible with abnormal cardiac development among SAM survivors during fetal and postnatal plastic periods.

Systemic Vascular Resistance

A key new finding is the elevated estimated SVR (peripheral resistance) in SAM survivors. A raised SVR suggests relative resistance vessel constriction and reduced density of small resistance arteries. Neither was measured directly here, but vasoconstriction and reduced small arterial density are consistent with reports in models of hypertension

from animals²⁸ and in humans.²⁹ The relationship between higher SVR and smaller LVOT (Figure 1) may arise from structural or from additional physiological factors. The first would follow the proposal that the abnormal SVR is because of underdevelopment of the arterial tree; alternatively, it may be a compensatory mechanism to preserve perfusion of some organs in the face of reduced CO. One consequence of diminished tissue level perfusion may be reduced aerobic capacity related both to reduced muscle blood flow in exercise and to the smaller size of the skeletal muscle mass itself noted in some survivors; we do not have data on aerobic capacity or physical performance in these subjects or in their controls. Whatever its origin, increased SVR and diastolic

Table 4. Relationships Between Cardiac and Large Artery (Carotid) Parameters as Indices of Remodeling

Cardiac Parameter	Nonoedematous n=46		Oedematous n=44–54		Controls n=35–39	
	cCSAi	cCSAii	cCSAi	cCSAii	cCSAi	cCSAii
Partial r (P value)						
LVEDV	0.26 (0.08)	0.29 (0.05)*	0.20 (0.17)	0.15 (0.3)	0.18 (0.28)	0.18 (0.31)
LVMI	0.35 (0.01)*	0.47 (0.001)*	0.22 (0.1)	0.28 (0.04)*	0.09 (0.6)	0.12 (0.5)
MVR	0.33 (0.02)*	0.32 (0.03)*	0.14 (0.35)	0.1 (0.5)	−0.1 (0.6)	−0.14 (0.43)

CSAi is age/sex-adjusted only, CSAii is age/sex/height, and weight adjusted. CSA indicates cross-sectional area; LVEDV, left ventricular end-diastolic volume; LVMI, left ventricular mass index; and MVR, mass/volume ratio.

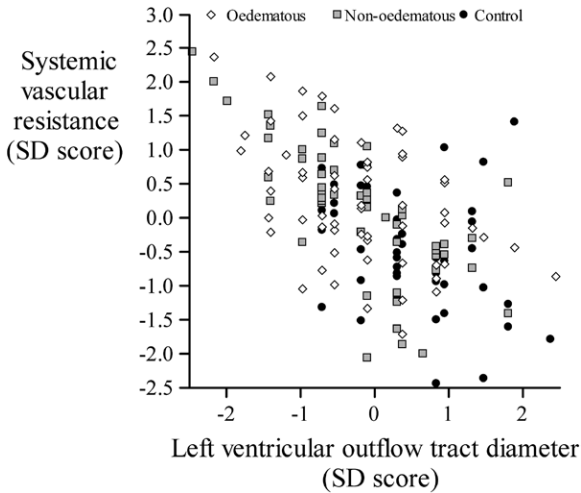


Figure 1. Plot of systemic vascular resistance against left ventricular outflow tract diameter in severe acute malnutrition survivors and controls.

BP put SAM survivors at higher risk of developing hypertension than controls.

Diastolic Blood Pressure

SAM survivors had similar systolic but higher diastolic blood pressures than controls. This may reflect higher sympathetic drive and arteriolar constriction, in line with elevated SVR and consistent with the literature on enhanced adrenergic³⁰ and

hypothalamic-pituitary-adrenal^{31,32} axes in adults with a lower birth weight, or in our hypothesis, a smaller total vascular network. In one Bogalusa cohort, black/white differences in birth weight, childhood growth, and BP in childhood largely explained BP in adolescence.³³ Thus, there are several specific pathways through which SAM during early childhood may alter further development and may impair later cardiovascular and metabolic function.

Remodeling of Large Vessels and Cardiac Indices

It is unsurprising in patients aged 30 years that neither cardiac nor large-vessel remodeling was found. However, the only finding that differed between case types is that the carotid cross-sectional area was more closely related to each LV index in adult marasmus survivors than in kwashiorkor survivors or in controls (Table 4). This finding elicits an additional hypothesis that these adaptations may lead to greater cardiac and vascular pathology in later life in the marasmus survivors when compared with either other group. We continue to follow them up.

PWV and Augmentation Index

Survivors had lower PWV and similar augmentation index when compared with controls, indicating less arterial stiffness using our standard adjustment (if body surface area as height^{1.7} was used, then PWV difference became lower, still in the same direction but no longer significant). The data for using height^{1.7} come from a European population, perhaps not appropriate to this survivor cohort here. We had hypothesized the opposite, based on reports of lower elastin content in arteries from individuals with lower birth weight.³⁴ Carotid-femoral PWV is an independent predictor of cardiovascular mortality, and is more powerful than, and displaces BP in predicting events,^{35,36} including in this population group.¹⁷ It is likely to be related to arterial calcification and sclerosis.^{15,37,38} It may be relevant that earlier work reported an impressive inverse relationship between maternal systolic BP and neonatal PWV³⁹; unfortunately, there are no maternal data.

Adjustment for mean pressure and heart rate did not alter these relationships. In addition, adjusting for visceral fat mass that is related to endothelial dysfunction and hence arterial stiffness did not explain the differences. The relatively young age of the cohort may underlie the lack of changes in arterial stiffness. Thus, longer term surveillance of SAM survivors will be essential to understand their risk of vascular disease more fully.

Carotid and Femoral IMT

The carotid IMT was not increased in survivors of SAM, suggesting no early atherosclerosis related to the nutritional insult. However, femoral IMT was greater in controls than in SAM survivors. Such an increase is likely to be unrelated to atherosclerosis because in more muscular arteries, such as the common femoral, IMT can be more influenced by an increased medial layer, which has not been shown to be a marker of generalized atherosclerosis.⁴⁰

Comparisons of Kwashiorkor and Marasmus

There were no significant differences between oedematous and nonoedematous SAM survivors in any cardiovascular measure. However, it is clear that whatever the underlying pathways,

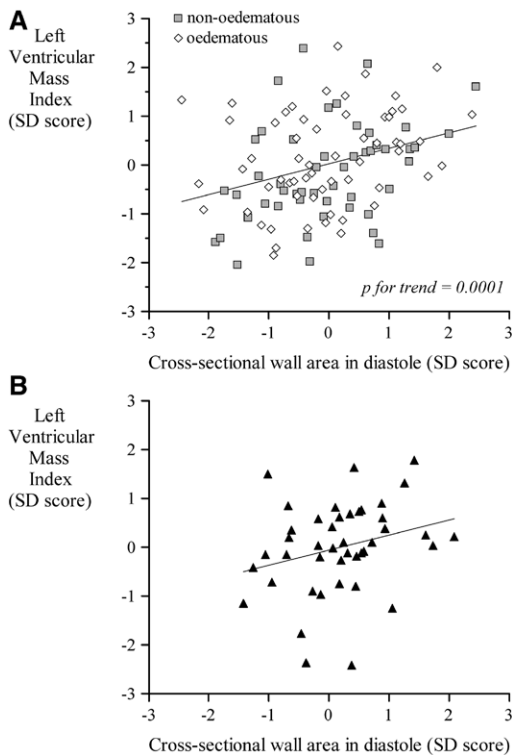


Figure 2. Left ventricular mass index (LVMI) SD, unadjusted, was related to diastolic carotid wall cross-sectional area in **A** all former cases as $LVMI\ SD = 0.017 + 0.32(\beta) (SE, 0.09) \times \text{carotid diastolic cross-sectional area}$; adjusted for age and sex, β became 0.23 (SE 0.09), $P = 0.012$. Further adjusting for height and weight, the relationship strengthened with $\beta = 0.25 (0.09)$, $P = 0.005$, so size contributed significantly more than just LVMI. **B**, Similarly in controls.

both clinical presentations in SAM are associated with greater cardiovascular risk. The prevention of SAM in children will, therefore, confer both short- and long-term benefits.

Limitations

Limitations here include the relatively small size of the control group, balanced by it being carefully community based; however, that choice of controls may also minimize differences because their gestational and childhood nutritional and other exposures are unlikely to have been optimal. All participants were still relatively young. A possible survivor-bias effect should be minimal because the overall mortality rate of treated cases in this age group in our unit was $\approx 4\%$ in the period when the subjects were born.

Perspectives

Survivors of SAM had smaller LVOT, reduced CO, higher diastolic blood pressure, and hence much greater SVR when compared with controls. Large-vessel remodeling was as yet minimal and not different. Carotid diastolic cross-sectional areas were related to LV indices, most prominently in the former overt marasmic survivors. This may have long-term cardiovascular consequences for the many people in the world who have experienced severe childhood malnutrition.

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Disclosures

None.

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Novelty and Significance

What Is New?

- The burden of disease related to childhood malnutrition arises from premature mortality and poor mental development with consequent poorer school performance in childhood and economic performance when individuals enter the labor force. The findings in this study highlight a potentially large additional burden from cardiovascular disease in adulthood.

What Is Relevant?

- If a greater risk of hypertension and its sequela are heralded by the increased peripheral resistance inferred in this study, then attention should be placed on interventions in early life to mitigate these risks.

Summary

Malnutrition in childhood increases pediatric morbidity and mortality. It is likely that the same early nutritional insult increases morbidity and mortality from hypertension and sequela in adulthood.