Original Article

Echocardiography of the right ventricle in infancy: Do early feeding practices make a difference?

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ABSTRACT

Background: It is important to understand the role of various feeding practices during infancy on the development of the cardiac structures, to intervene early with the prevention of cardiovascular disease. **Aim:** The aim of the study was to compare the structures and functions of the right side of the heart in exclusively breastfed (EBF) and formula fed (FF) babies in the 1st year of life. **Methods:** A cross-sectional study was conducted for 76 healthy infants aged 3–24 months of life of whom 38 were EBF and 38 were FF in the first 6 months of life. The right ventricular functions and dimensions of the chamber were assessed by echocardiography. The measurements included percent fractional shortening (%FS), right ventricular velocity time integral (RV-VTI), cardiac output, and tricuspid annular plane systolic excursion (TAPSE), e prime, and s prime. **Results:** Mean values of %FS for right side were significantly higher in EBF infants in 51.33±5.20 than in FF infants (49.22±3.75) at $p<0.05$. There was a significant increase in mean RV VTI values in EBF infants (17.2±2.73) than FF infants (15.9±1.94) $p<0.01$. We noticed significant increase (Cardiac Output) in EBF infants (5.81±1.01) than FF infants (5.26±1.18). TAPSE was significantly higher in EBF infants (1.56±0.18) than FF infants (1.46 ±0.20) at $p<0.05$. **Conclusion:** EBF in infancy supports higher performance of the right side of the heart in infancy.

Key words: Breastfeeding, Cardiac function, Echocardiography, Formula feeding, Infancy, Right ventricle

Cardiovascular disease (CVD) is the leading cause of death worldwide. Prevention of death from CVD starts early in infancy and is influenced by the mode of feeding [1]. Emerging research is showing the protective effect of breastfeeding and the negative effects of early feeding with cow's milk based formula milk on the development of CVD [2,3]. However, the mechanism by which various feeding methods influence the development of the heart or the increased susceptibility to CVD is poorly understood.

The period of early infancy is characterized by a high growth and developmental rates especially for organs such as the heart and suboptimal diet during this period may permanently affect cardiovascular development [3]. Hence, the patterns of nutritional exposures during infancy have an essential role in the cardiovascular development and associated CVD that may occur in adulthood as a result of early poor feeding practices [1,2].

Studies on the cardiovascular developmental changes in early infancy related to mode of feeding have been done for infants and children [4] but not in relation to mode of feeding. Studies have shown that echocardiography is a useful method for assessing the cardiovascular structures of the heart [4,5]. Hence, there is a need to examine the cardiac structural and functional changes during infancy in relation to mode of feeding. This could have important implications in the prevention of CVD. The aim of this study was to compare cardiovascular structures and function of right chamber of the heart in exclusively breast-fed (EBF) and formula-fed babies in the 1st year of life.

MATERIALS AND METHODS

This cross-sectional case–control study was conducted between October 2018 and June 2019 in the Pediatric Department outpatient clinic of Benha University Hospital in Cairo (Egypt). The children were selected from the OPD and cardiac functions and dimensions in EBF infants were compared with the infants who were not breastfed, that is, formula fed (FF). The study was approved by Ethics Committee of Faculty of Benha University. Confidentiality was taken in consideration using code number cod refer to name of the baby. Verbal informed consents were obtained from parents of all subjects of the study.

This study was carried out for 76 infants aged from 3 to 12 months, this was divided into two groups: Group (I): 38

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EBF infants and Group (II): 38 FF infants. Healthy full-term babies, from birth until age of 1 year, both male and female, and exclusively breastfeeding or formula feeding from birth, were included in the study. Exclusion criteria were infants with major congenital anomalies, neurological disorders, acute or chronic diseases (as renal or blood, endocrine, or metabolic disorders), babies on medications (other than vitamins or minerals) or exposed to irradiation, and congenital heart disease.

Anthropometric studies

Anthropometric measurements for weight and supine length were done by standard methods to calculate the body mass index (BMI) which was used as an indicator of overweight or obesity and was calculated from weight in kg by length squared in meters [6]. General and systemic examination for heart and chest were done to exclude any abnormality.

Echocardiography studies

Cardiac output (CO), heart rate (HR), and body surface area (BSA) were estimated by standard methods. Echocardiography measurements included right ventricular diameter (RVd mm), right ventricular out tract diameter (RVOT mm), right ventricular velocity time integral (RV VTI/cm), tricuspid annular plane excursion (tricuspid annular plane systolic excursion [TAPSE]), percent fractional shortening (%FS), or %fractional area change (%FAC) were measured using methods recommended by the American Society of Echocardiography [7]. Right ventricular mass (RV mass) was computed using the formula derived by: (4/5 Pi D1D2L) [4,5]. Two-D, M-mode, continuous pulsed, and color Doppler echocardiography were performed with standard sweeps including subcostal, parasternal, apical, and suprasternal views. Missing echocardiograms were mainly due to crying behavior or unavailability of equipment or absence of sonographer [8,9].

Statistical analysis

The collected data were tabulated and analyzed using SPSS version 16 software (SPSS Inc, Chicago, ILL Company). Categorical data were presented as number and percentages, Chi square, and Fisher's exact test were used to analyze them. Quantitative data were tested for normality using Shapiro-Wilks test assuming normality at $p>0.05$. Normally distributed variables were expressed as mean ±standard deviation (SD) and analyzed by Student "*t*"-test for two independent groups. Correlation studies were done using Pearson correlation for bivariate analysis. $p\leq 0.05$ was considered cutoff of significance.

RESULTS

Table 1 shows the epidemiological data of the population of infants under study in relation to age, sex, and mode of feeding. There were significant differences between the different parameters studies between the breastfed or FF groups ($p>0.05$).

There was no difference in BSA or HR between the breastfed and FF infants. However, COP was significantly higher in breastfed infants (5.81±1.01) than artificially fed infants (5.26±1.18) ($p=0.036$), as demonstrated in Table 2.

Table 3 shows that there was significant increase in FS % in EBF infants (51.33±5.20) than in FF infants (49.22±3.75), RV VTI ($p=0.02$), and TAPSE ($p=0.041$). Table 4 demonstrates that there was no significant difference in all parameters measures in-between males and females in both breastfed and FF infants under 1 year of age.

Table 5 presents correlations between BSA and the studied Echo parameters for the right ventricle in breastfed and artificially fed under 1-year of age. There were highly significant correlations in breast fed and FF fed with BSA and %FS (r0.6 at $p=0.001$ and r0.5 at $p=0.002$, respectively), TAPSE (r0.5 at $p=0.002$ and r0.5 at $p=0.002$, respectively), and RVOT (r0.5 at $p=0.001$ and r0.6 at $p=0.001$, respectively) but not with RV mass, E cms E/A ratio in both breastfed, and FF infants under 1-year of age $p>0.05$.

Table 6 presents correlations between BMI and the studied Echo parameters in breastfed and artificially fed infants. There were significant correlations in FF fed with BMI and RV mass (r0.4 at $p=0.015$), %FS (r0.4 at $p=0.03$), and RVOT (r0.4 at $p=0.01$) but not with other parameters. BMI correlated with RV VTI in breastfed (r0.4 at $p=0.03$) but not with other parameters under study.

DISCUSSION

In this cross-sectional study, among healthy children in first 24 months of life of both sex, we found that FS% values in EBF infants were significantly higher than FF infants; although, both were within the normal range. Percent FS has been suggested to be a reliable echocardiographic marker of RV function [10].

Table 1: Epidemiological data of infants under study

Variable		Breast fed (n=38)		Artificially fed (n=38)		Test of significance	p
Age (months)	Mean±SD	7.6±3.08		7.5±2.9		St. "t"= 0.081	0.93 (NS)
	Range	3–12		3–12			
		No.	**%**	**No.**	**%**	**χ^2**	**P**
	≤6 m	16	44.4	16	42.1	0.041	0.84 (NS)
	>6 m	20	57.9	22	57.9		
Sex	Male	14	38.9	19	50.0	0.92	0.33 (NS)
	Female	22	61.1	19	50.0		

Table 2: Comparison of body surface area, heart rate, and COP in breastfed versus formula fed infants under-1 year of age

Variable	Breast fed (n=38)			Artificially fed (n=38)			F-ratio	p-value
	Mean	±SD	Range	Mean	±SD	Range		
BSA	0.395	0.046	0.31–0.48	0.388	0.045	0.27–0.47	0.67	0.51 (NS)
HR (b/min)	119.3	7.49	100–132	120.5	7.79	100–140	0.67	0.51 (NS)
COP (l/min)	5.81	1.01	3.89–7.98	5.26	1.18	3.03	2.14	0.036 (S)

BSA: body surface area, HR (b/min): Heart rate beats per minute, COP l/m: Cardiac output liters per minute, Cutoff level of significance <0.05, S: Significant, NS: Not significant

Table 3: Comparison of echocardiographic right ventricular dimensions and functions in breastfed versus artificially fed infants

Variable	Breast fed (n=38)			Artificially fed (n=38)				p-value
	Mean	±SD	Range	Mean	±SD	Range		
RT.V. mass	5.13	1.02	0.45–6.05	5.15	0.71	3.7–6.8	0.10	0.91 (NS)
%FAS	51.33	5.20	43.5–63.6	49.22	3.75	43–60	2.007	0.049 (S)
E cm/s	80.5	10.64	60–96.5	83.1	9.26	67–97	1.1	0.27 (NS)
E/A	1.30	0.15	1.1–2.0	1.31	0.17	1.1–2.1	0.43	0.67 (NS)
TAPSE/cm	1.56	0.18	1.1–2.0	1.46	0.20	1.1–2.0	2.08	0.041 (S)
RVOT mm	1.29	0.085	1–1.4	1.28	0.099	1–1.5	0.43	0.67 (NS)
RV VTI/cm	17.2	2.73	13.3–27.0	15.9	1.94	12.1–20.0	2.34	0.022 (S)
RV d/cm	1.31	0.11	1.1–1.7	1.27	0.09	1.1–1.5	1.24	0.21 (NS)

RT.V: Right ventricular, FAS: Percent fractional area shortening, RVOT: Right ventricular out tract diameter, RV VIT: Right ventricular velocity time integral, TAPSE: Tricuspid annular plane excursion. Cutoff level of significance <0.05, S: Significant, NS: Not significant

Table 4: Echo parameters according to sex among breastfed and artificially fed infants

Variable	Males (n=19)		Females (n=19)		F-ratio	p-value*
	Mean	±SD	Mean	±SD		
Formula fed						
RT.V. mass	5.24	0.68	5.06	0.74	0.79	0.43
FAC%	52.06	5.46	50.18	4.71	1.06	0.29
E cm/s	80.76	10.62	80.20	11.05	0.15	0.88
E/A	1.31	0.13	1.31	0.20	0.103	0.92
TAPSE/cm	1.52	0.18	1.59	0.18	1.08	0.28
RVOTd/cm	1.29	0.11	1.27	0.08	0.47	0.64
RV VTI/cm	18.09	3.12	16.42	2.01	1.95	0.059
RV d/cm	1.29	0.10	1.25	0.08	1.31	0.19
Breastfed						
RT.V. mass	5.38	0.58	4.74	1.40	1.92	0.064
FAC%	52.06	5.46	50.18	4.71	1.06	0.29
E cm/s	80.76	10.62	80.20	11.05	0.15	0.88
E/A	1.31	0.13	1.31	0.20	0.103	0.92
TAPSE/cm	1.50	0.20	1.40	0.18	1.43	0.16
RVOTd/cm	1.30	0.07	1.27	0.10	0.95	0.34
RV VTI/cm	16.04	2.19	15.83	1.54	0.31	0.75
RV d/cm	1.29	0.10	1.32	0.13	0.77	0.44

RT.V: Right ventricular, FAS: Percent fractional area shortening, RVOT: Right ventricular out tract diameter, RV VIT: Right ventricular velocity time integral, TAPSE: Tricuspid annular plane excursion. *Cutoff level of significance <0.05, S: Significant, NS: Not significant

Differences in %FS or shortening have been poorly studied in relation to early feeding practices in EBF versus FF infants. Normal values range from 43±18%, and a value <35% is indicative of RV systolic dysfunction [11]. Several recent studies have successfully utilized RV FS% by echocardiography to monitor RV function in both neonates and children with congenital heart disease, pulmonary hypertension, and sickle cell anemia [4,12,13].

Table 5: Correlation between body surface area and the echo parameters in breastfed and artificially fed infants

BSA with	Breast fed (n=38)		Artificially fed (n=38)	
	R	p	R	p
RT.V. mass	0.233	0.17	0.233	0.17
FAC%	0.592	<0.001 (HS)	0.483	0.002 (S)
E cm/s	0.219	0.199	0.062	0.71
E/A	−0.165	0.33	0.306	0.061
TAPSE/cm	0.501	0.002 (S)	0.516	=0.001 (HS)
RVOTd/cm	0.539	=0.001 (HS)	0.645	<0.001 (HS)
RV VTI/cm	0.771	<0.001 (HS)	0.204	0.22
RV d/cm	0.167	0.33	0.312	0.056

RT.V: Right ventricular, FAS: Percent fractional area shortening, RVOT: Right ventricular out tract diameter, RV VIT: Right ventricular velocity time integral, TAPSE: Tricuspid annular plane excursion. Cutoff level of significance <0.05, S: Significant, NS: Not significant

In children, there is controversy about the reliability of RV FS as a marker of RV EF and its use in the assessment of RV systolic function. Some studies suggested that the RV FS % was decreased in children who developed pulmonary arterial hypertension as compared to a control cohort [14]. There were studies that suggested that a lower RV FS was independently associated with transplantation in infants with hypoplastic left heart syndrome, [4].

The significant increase CO in EBF infants in our study as compared to FF infants suggests that the increase in the %FS could have been the underlying cause. This reflects a more active cardiovascular system in the EBF infants to meet their needs of growth and development, particularly for the rapidly growing structures of the brain. Our study found a mild decrease in the HR of EBF infants compared to the FF infants but without significant

Table 6: Correlation between body mass index (BMI) and the studied echo parameters in breastfed and artificially fed infants

BMI with	Breast fed (n=38)		Artificially fed (n=38)	
	r*	P	r	P
RT.V. mass	0.08	0.61	0.393	0.015 (S)
FAC%	0.326	0.053	0.358	0.027 (S)
E cm/s	0.064	0.71	0.306	0.062
E/A	−0.115	0.50	0.184	0.26
TAPSE/cm	0.238	0.16	0.232	0.16
RVOTd/cm	0.157	0.36	0.401	0.013 (S)
RV VTI/cm	0.357	0.032 (S)	0.110	0.51
RV d/cm	0.033	0.84	0.064	0.70

RT.V: Right ventricular, FAS: Percent fractional area shortening, RVOT: Right ventricular out tract diameter, RV VIT: Right ventricular velocity time integral, TAPSE: Tricuspid annular plane excursion. *r: Pearson correlation, P: p-value level of significance (two-paired significance), cutoff p<0.05 (S)

differences. This probably reflects a tolerance mechanism that enables them to increase their reserve under stressful situations.

We found that there was a significant increase in mean RV VTI values in EBF infants. There were studies that suggested evaluating VTI in relation to HR because of strong negative correlations between VTI and HR [15-17]. In accordance with this, there was another study that showed a negative correlation, particularly in children <7 years of age [18]. This relationship is likely caused by a predominantly frequency-based regulation of CO and becomes less obvious in larger ventricles that are also able to vary their systolic volume using the Frank-Starling mechanism [19]. The product of VTI and HR (VTI×HR), also called MD, compensates for the fact that VTI values at low HRs will result in comparable CO with those of low VTI values at high HRs [18].

In our study, we found a significant increase in mean TAPSE values in EBF infants compared to FF infants. TAPSE is a good indicator of RV function and indicates a superiority of RV function in infants who are EBF. Furthermore, there was a positive correlation between TAPSE and age in both EBF infants (r0.45, p=0.006) and FF infants (r0.6, p≤0.001), and a positive correlation between TAPSE and BSA in both EBF infants (r0.5, p=0.002) and FF infants (r0.5, p=0.001); although, no significant difference was identified between male and female infants in both groups. To the best of our knowledge, we found no studies that reported differences in RV TAPSE in related to EBF versus FF but irrespective to feeding there was a study that suggested evaluating mean TAPSE values in relation to age group, height, weight, BMI, and BSA. BSA showed a strong positive correlation with TAPSE values [20]. There was another study that had showed TAPSE values with a positive correlation with increasing age and BSA, with no significant differences between sexes [21]. Another study evaluated TAPSE values in relation to gestational age, infant's age, weight, and sex and showed that body weight and weeks of gestation were strongly positively correlated with TAPSE values with no significant differences between sexes [22]. Similarly, TAPSE values were found to be correlated to BSA with no significant differences in TAPSE values between males and females [23]. It is still possible that more detailed functional cardiovascular measurements, such as endothelial dysfunction, arterial stiffness, right or left ventricular diastolic filling patterns, might be influenced by breastfeeding [24].

The current study showed that the TAPSE and RV-VTI were significantly high in EBF infants. This indicates the RV functions were more developed and optimal in the EBF especially that FS% was also high in the EBF infants. The finding of higher RV FS% in EBF results in higher blood flow to the lungs, enhancing oxygenation of blood returning from the body structures, this also indicates, the RV function is more superior in the EBF than in the FF. This can be explained by the fact that breastfeeding is an active process whereas FF is passive and does not require more effort by the infant [25].

There were significant correlations between BMI and RV mass and FS among FF and RV VTI in breastfed. The significance of these findings is difficult to interpret, but since BMI is an indicator of overweight or increased size of the child, it is thereby expected that RV mass and %FS would be increased with increased size of child. Among breastfed the correlation with RV VTI may be an adaptive change to overcoming pulmonary tissue resistance caused by overweight. A study conducted to assess oxygen saturations in breastfed and FF, showed that breastfed had higher oxygen saturations and thereby better oxygenation of their tissues and organs particularly to the rapidly growing brain [26].

A study of the left ventricular echo parameters in infants <2 years of age showed that left ventricular mass was higher in overweight and obese children while %FAC was higher in obese but not overweight as compared to normal children of the same age. The research team concluded that such findings indicate that ventricular mass adapts to needs of lean body mass, which can be assumed to interpret the findings in our study [27]. Since increases in ventricular mass correlate with high BP and in the case of the RV with pulmonary hypertension; hence, this can be taken as a flag sign for children with increased risk of pulmonary hypertension and can explain the increased risk of FF infants to develop respiratory disease.

The values were significant even after adjusting infant sex, gestational age-adjusted SD scores for age and anthropometric study, maternal age, parity, maternal cardiovascular risk factors, family history for CVDs, pregnancy complications, and paternal smoking status. The European study on echocardiographic data [28] of over 2000 healthy children reported no significant differences in echocardiographic values for the left ventricle between the sexes. The previous studies have studied cardiovascular structures in relation to age, height, weight, and BSA [28,29].

The strength of this study is the availability of detailed information about the duration and exclusivity of breastfeeding. This enabled us to investigate the influence of EBF in first 6 months of life on the cardiac functions using FF infants as a control group. However, we found no studies that reported differences in cardiac dimensions related to EBF versus FF infants. Hence, to the best of our knowledge this is the first study that reports such findings. However, there was a study that suggested early nutrition may already influence cardiovascular structures and functional development from early childhood onward [30].

Various other studies have shown a significant association between breastfeeding in infancy and biomarkers that predict later development of CVD [31]. The current study supports these previous studies and show that RV functional and dimensional differences between EBF and FF could be a pointer to increased susceptibility to cardiac disease. It appears that breastfeeding increases tolerance to stresses that may compromise the right side of the heart as pulmonary disease or hepatic or right-sided cardiac anomaly in infants and children. It thereby supports child survival and optimizing child growth and development and resilience to later stresses in life.

Encouraging mothers to breastfeed exclusively in the first 6 months of life can influence optimal development of cardiac functions in early life and decrease the risk of CVD in later adulthood life. Restricting formula feeding in early life to rare medical conditions is beneficial to both mother and child. However, these children who are exposed to formula need to be followed up for cardiac functions in later life; especially, if obese. Optimal early feeding practices need to be supported by healthy life styles in later years such as healthy diet, physical exercise, and avoidance of exposure to smoking and non-stressful life.

A potential limitation of the study is that the associations between breastfeeding and right cardiac structures may depend on additional dietary patterns. In the analysis, we did not adjust for other components of infant diet. Another limitation was that because of the young age at examination and the limited time available at the visits, we were not able to get a higher percentage of successful cardiovascular measurements as left side of the heart.

CONCLUSIONS

The results from this cross-sectional study suggest that early developmental changes in the right side of the heart can be influenced by the feeding patterns in infancy. These changes are not influenced by sex, but by BSA and BMI. Further research is required to replicate these findings and to investigate whether, and to what extent, these changes contribute to an increased risk of CVD in later life.

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