



Correlation between Blood Pressure and Left Ventricular Function in Neonates: A Retrospective Observational Study

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ABSTRACT

Purpose: Ejection fraction, measured as the fraction of blood ejected from the ventricle in each heartbeat using M-mode echocardiography, serves as a primary indicator of left ventricular systolic function. This study explores the correlation between blood pressure and left ventricular systolic function in neonates using M-mode echocardiography.

Methods: Neonates who underwent echocardiography in the neonatal intensive care unit between January 2011 and December 2020 were retrospectively studied.

Results: Our analyses showed a significant association between ejection fraction and systolic blood pressure, but not with diastolic or mean blood pressure—both of which are more sensitive to hypotension. Ejection fraction was also not significantly associated with heart rate, urine output, or inotropic support in this study, suggesting that factors influencing urine output may not directly relate to ejection fraction. Additionally, we found that higher systolic blood pressure was correlated with advanced gestational age, the absence of patent ductus arteriosus, and no need for fentanyl administration. Notably, lower gestational age and lack of mechanical ventilation were both associated with increased hourly urine output, suggesting that developmental maturity and respiratory stability may influence renal function.

Conclusion: Neonatal hypotension occurred secondary to decreased systolic cardiac function and peripheral vascular resistance. Neonatologists should carefully monitor the individual components of blood pressure and prescribe medications accordingly, considering that systolic blood pressure is correlated with ejection function.

Key Words: Blood pressure; Echocardiography; Hypotension; Neonate

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INTRODUCTION

Neonatal hypotension is a common condition/disorder encountered in the neonatal intensive care unit (NICU)¹⁾. However, its definition, diagnosis, treatment, and prognosis remain controversial, and there is a lack of consensus among clinicians regarding its influencing factors²⁾. Myocardial dysfunction and abnormal peripheral vasoregulation during the transitional period are the most common causes of hypotension in neonates³⁾.

In the NICU, targeted echocardiography is used to detect heart disease and assess cardiac function⁴⁾. Following technological advancements, several tools have been developed to evaluate the cardiac function in children and adults. However, portable echocardiography has limited applicability for thorough cardiac evaluation in neonates because of their small size and relatively unstable condition. Despite the limitations of echocardiographic equipment, M-mode assessment remains rapid, easily applicable, and highly reliable, making it the preferred method for evaluating the ejection fraction (EF) in critically ill neonates.

Our research was initiated to determine which treatment is most appropriate when hypotension develops in newborns. There are several causes of low blood pressure; however, in newborns, the most common treatment for hypotension involves the provision of a volume of inotropes. Therefore, we aimed to determine whether echocardiography results were helpful in determining the cause of hypotension and whether using inotropics improved EF in such patients. Furthermore, we aimed to identify the correlation between EF and blood pressure in neonates using M-mode echocardiography and investigate the factors that may influence neonatal hypotension.

MATERIALS AND METHODS

1. Subjects

We retrospectively investigated neonates who underwent echocardiography after admission to the NICU of Chung-Ang University Hospital, Seoul, Korea, between January 2011 and December 2020. Neonates diagnosed with significant congenital heart disease, arrhythmia, culture-proven sepsis, congenital metabolic diseases, congenital hypothyroidism, or fetal hydrops were excluded.

Infant data included gestational age (GA), birth weight, sex, type of delivery, and diagnosis of neonatal diseases such as respiratory distress syndrome (RDS) or patent ductus arteriosus (PDA). RDS is clinically defined as a disease entity that presents with respiratory difficulties, including tachypnea, or the need for oxygen therapy and mechanical ventilation, and is evident on chest radiographs as an air bronchogram with decreased lung expansion⁵⁾. PDA was defined as symptomatic when treated with indomethacin or ibuprofen, or surgically repaired with associated symptoms (continuous or systolic murmur, low diastolic blood pressure [DBP], wide pulse pressure, hypotension, bounding pulse, increased serum creatinine concentration, or oliguria) within 7 days of birth⁶⁾.

Echocardiographic examinations were performed by a pediatric cardiologist using a Philips HD11XE (Philips) device in an NICU setting. M-mode parameters included interventricular septal thickness at end diastole, left ventricular internal diameter at end diastole, left ventricular internal diameter at end systole, left ventricular posterior wall at end diastole, aortic root diameter (Ao), left atrial diameter (LA), LA/Ao ratio, and the EF, were automatically calculated. For echo parameters, an M-mode examination was performed on the parasternal long-axis view. From the information simultaneously recorded at the time of echocardiographic examination, factors thought to be related to EF (systolic blood pressure [SBP], DBP, heart rate [HR], and urine output [UO]) were identified. UO was assessed based on the 24-hour UO on the day of echocardiography. Blood pressure was continuously monitored using an arterial line or measured using oscillometry with an appropriately sized cuff placed around the infant's biceps (CARESCAPETM Monitor B650; GE Healthcare). Hypotension was defined as a mean blood pressure (MBP) lower than the GA. Diagnosis of decreased cardiac contractility (low EF) was made when EF is lower than 55% (EF normal range, 55% to 75%). Moreover, we investigated the medications administered to these neonates, primarily those that may influence blood pressure, including inotropes, fentanyl, morphine, and aminophylline/caffeine. Inotropes included dopamine, dobutamine, vasopressin, epinephrine, and milrinone.

The primary objective of this study was to determine how EF is direct relationship between EF and blood pressure, HR, and UO, and the secondary objective was to determine the extent to which inotropes affected EF.

The study protocol was reviewed and approved by the Insti-

tutional Review Board of the Chung-Ang University Hospital (IRB No. 1708-003-16087). All studies were performed in accordance with relevant guidelines and regulations.

2. Statistical analyses

The Shapiro-Wilk test was used to test the normality of the variables. While SBP and DBP passed the Shapiro-Wilk (normality) test, MBP, GA in weeks, body weight, and EF did not. Additionally, we checked a quantile-quantile (q-q) plot that did not show a marked deviation from linearity. Therefore, we conclude that the normal distribution assumption for parametric tests was not violated.

Multiple linear regression with stepwise selection was used to assess the associations of SBP, DBP, and MBP with EF and several other variables. The independent variables were EF; GA in weeks; PDA; sex; need for mechanical ventilation; and the use of inotropes, fentanyl, aminophylline/caffeine, and/or morphine.

Factors with *P*-values <0.1 on univariate analysis were further investigated using multivariate analysis. To avoid multicollinearity, the GA weeks were selected as the GA weeks and body weight. In addition, the multicollinearity test was not associated with any difficulty (condition indices <30, variance inflation factor values <10) between the independent variables chosen in this study. Statistical significance was set at *P*<0.05.

All statistical analyses were performed using the SPSS software version 23.0 (IBM Corp.).

RESULTS

Among the 1,191 echocardiograms, 55 performed after 7 days of life were excluded. The remaining 1,136 echocardiograms were used in this study. The mean±standard deviation GA of the cohort was 34.8±4.0 weeks, and the mean birth weight was 2,404.9±876.5 g. The male-to-female ratio was 53.4% to 46.6%. A total of 760 neonates (68.6 %) were delivered via cesarean section. Mechanical ventilation was required for 394 patients (34.7%). Fentanyl was administered in 195 patients (17.2%), morphine in 43 patients (3.8%), and aminophylline and/or caffeine in 219 patients (19.3%). RDS was diagnosed in 253 patients (22.3%) and PDA in 415 patients (36.5%). The mean age at which echocardiograms were obtained was 3.4±1.6 days of life.

Among the 1,191 echocardiograms, 55 performed after seven days of life were excluded. Among the 1,136 remaining echocardiograms, 86 showed low EF and 1,050 showed normal EF. Only 11 (12.8%) patients with low EF had actual hypotension, whereas 59 (5.6%) with normal EF had hypotension (Table 1).

We assessed the correlations between EF and SBP, DBP, and MBP using M-mode echocardiography and found that EF

Table 1. Baseline Demographic and Clinical Features of the Enrolled Participants

Variable	Total (n=1,136)	Low EF (n=86)	Normal EF (n=1,050)	<i>P</i> -value
Gestational age (wk)	34.8±4.0	33.7±4.1	34.9±3.9	0.130
Birth weight (g)	2,398.7±873.4	2,150.4±866.4	2,431.9±875.7	0.046
Male sex	605 (53.4)	46 (55.4)	559 (54.8)	0.913
Cesarean section	760 (66.9)	62 (72.1)	698 (66.9)	0.326
Echocardiography (d)	3.3±1.6	2.9±1.4	3.4±1.6	<0.001
Hypotension	70 (6.2)	11 (12.8)	59 (5.6)	0.008
RDS	253 (22.3)	22 (25.6)	231 (22.1)	0.460
PDA	415 (36.5)	40 (46.5)	375 (36.0)	0.051
Ventilator care	394 (34.7)	34 (39.5)	360 (34.6)	0.355
Inotropics	141 (12.4)	25 (29.1)	116 (11.1)	<0.001
Volume infusion	112 (9.9)	20 (23.3)	92 (8.8)	<0.001
Aminophylline/caffeine	219 (19.3)	17 (19.8)	202 (19.3)	0.915
Fentanyl	195 (17.2)	22 (25.6)	173 (16.5)	0.032
Morphine	43 (3.8)	3 (3.5)	40 (3.8)	0.877
Heart rate (bpm)	140.7±16.0	145.6±19.2	140.2±15.8	<0.001
Urination (cc/kg/hr)	3.2±1.4	2.8±1.2	3.2±1.4	0.142

Values are expressed as mean±standard deviation or number (%).

Abbreviations: EF, ejection fraction; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus.

was significantly associated with SBP in both univariate and multivariate analyses but not with DBP and MBP. Multivariate analysis showed that higher GA, absence of PDA, and lack of fentanyl and aminophylline/caffeine use were significantly correlated with higher SBP, whereas higher GA, absence of PDA, and lack of fentanyl and aminophylline/caffeine use were significantly correlated with DBP. MBP, considered a sensitive indicator of hypotension, significantly correlated with higher GA, absence of PDA, and no need for fentanyl administration or aminophylline/caffeine usage (Table 2). EF was also significantly associated with HR but not with UO in both univariate and multivariate analyses. The multivariate analysis revealed that lower GA and aminophylline/caffeine use were associated

with HR, whereas lower GA, absence of PDA, and lack of fentanyl and aminophylline/caffeine correlated with increased UO (Table 3). We further investigated the influence of EF on the inotropes (dopamine and dobutamine). As expected, EF showed no significant differences according to inotrope use, and this analysis included all study participants regardless of GA (Table 4).

Figure 1 shows the correlations of EF with SBP, DBP, and MBP. Only the EF and SBP were significantly correlated. There was also a correlation between the EF, HR, and UO. EF did not correlate with HR or UO.

Table 2. Correlation between Ejection Fraction and Blood Pressure

Ejection fraction	Univariate analysis				Multivariate analysis			
	B	SE	95% CI	P-value	B	SE	95% CI	P-value
SBP								
EF	0.092	0.034	0.026 to 0.158	0.007	0.063	0.028	0.009 to 0.118	0.022
GA (wk)	1.318	0.067	1.186 to 1.450	<0.001	1.184	0.087	1.014 to 1.355	<0.001
Male sex	-0.601	0.628	-1.833 to 0.631	0.339				
PDA	-6.724	0.608	-7.918 to -5.531	<0.001	-3.079	0.573	-4.204 to -1.953	<0.001
Ventilation	-7.778	0.602	-8.959 to -6.596	<0.001	-1.648	0.692	-3.005 to -0.290	0.017
Fentanyl	-10.516	0.750	-11.988 to -9.043	<0.001	-4.657	0.857	-6.337 to -2.976	<0.001
Aminophylline/caffeine	-5.078	0.762	-6.572 to -3.583	<0.001	3.392	0.810	1.803 to 4.981	<0.001
Morphine	-2.384	1.565	-5.455 to 0.686	0.128				
DBP								
EF	0.015	0.025	-0.034 to 0.065	0.548				
GA (wk)	0.806	0.053	0.702 to 0.910	<0.001	0.826	0.068	0.692 to 0.959	<0.001
Male sex	-1.302	0.467	-2.218 to -0.385	0.005				
PDA	-4.519	0.459	-5.419 to -3.619	<0.001	-2.579	0.459	-3.481 to -1.678	<0.001
Ventilation	-3.799	0.467	-4.716 to -2.881	<0.001				
Fentanyl	-5.323	0.584	-6.469 to -4.176	<0.001	-1.685	0.593	-2.849 to -0.521	0.005
Aminophylline/caffeine	-2.522	0.574	-3.649 to -1.396	<0.001	2.929	0.641	1.672 to 4.186	<0.001
Morphine	-0.371	1.169	-2.664 to 1.921	0.751				
MAP								
EF	0.041	0.029	-0.015 to 0.097	0.154				
GA (wk)	0.934	0.059	0.818 to 1.051	<0.001	0.898	0.075	0.750 to 1.046	<0.001
Male sex	-0.636	0.530	-1.677 to 0.404	0.230				
PDA	-5.487	0.514	-6.495 to -4.479	<0.001	-3.278	0.504	-4.268 to 2.288	<0.001
Ventilation	-4.482	0.528	-5.517 to -3.446	<0.001				
Fentanyl	-6.569	0.656	-7.855 to -5.282	<0.001	-2.436	0.658	-3.727 to -1.144	<0.001
Aminophylline/caffeine	-3.431	0.646	-4.699 to -2.163	<0.001	2.534	0.709	1.143 to 3.924	<0.001
Morphine	-1.019	1.320	-3.608 to 1.571	0.440				

Abbreviations: EF, ejection fraction; SE, standard error; CI, confidence interval; SBP, systolic blood pressure; GA, gestational age; PDA, patent ductus arteriosus; DBP, diastolic blood pressure; MAP, mean blood pressure.

Table 3. Correlation between Ejection Fraction and Heart Rate and Urine Output

Ejection fraction	Univariate analysis				Multivariate analysis			
	B	SE	95% CI	P-value	B	SE	95% CI	P-value
HR								
EF	-0.104	0.051	-0.205 to -0.003	0.043				
GA (wk)	-1.820	0.105	-2.026 to -1.614	<0.001	-1.553	0.135	-1.818 to -1.288	<0.001
Male sex	2.753	0.953	0.884 to 4.623	0.004	2.022	0.878	0.300 to 3.745	0.021
PDA	3.395	0.969	1.495 to 5.296	<0.001				
Ventilation	7.321	0.956	5.446 to 9.197	<0.001				
Fentanyl	7.933	1.208	5.562 to 10.303	<0.001				
Aminophylline/cafeine	13.214	1.113	11.030 to 15.398	<0.001	4.410	1.353	1.485 to 6.795	0.002
Morphine	-2.144	2.377	-6.807 to 2.520	0.367				
UO								
EF	0.007	0.004	-0.002 to 0.015	0.125				
GA (wk)	-0.074	0.010	-0.093 to -0.055	<0.001	-0.087	0.013	-0.112 to -0.062	<0.001
Male sex	0.216	0.081	0.056 to 0.375	0.008	0.185	0.078	0.032 to 0.338	0.018
PDA	-0.226	0.082	-0.387 to -0.065	0.006	-0.291	0.085	-0.458 to -0.124	0.001
Ventilation	-0.065	0.083	-0.227 to 0.097	0.434				
Fentanyl	-0.423	0.102	-0.624 to -0.222	<0.001	-0.651	0.109	-0.866 to -0.437	<0.001
Aminophylline/cafeine	0.651	0.097	0.461 to 0.842	<0.001	0.274	0.118	0.043 to 0.505	0.020
Morphine	-0.538	0.201	-0.932 to -0.145	0.007				

Abbreviations: SE, standard error; CI, confidence interval; HR, heart rate; EF, ejection fraction; GA, gestational age; PDA, patent ductus arteriosus; UO, urine output.

Table 4. Differences in Ejection Fraction Based on the Use of Inotropes

	Inotropes (-)	Dopamine	Dobutamine	Dopamine and dobutamine	P-value
EF	67.5±8.0	68.1±10.0	56.8±8.3	65.5±8.7	0.052

Values are expressed as mean±standard deviation.

Abbreviation: EF, ejection fraction.

DISCUSSION

Overall, our study found that EF was not correlated with MBP, a sensitive clinical indicator of blood pressure, although it was correlated with SBP. Additionally, inotropes did not affect the EF. Although it has been hypothesized that inotropes may influence EF, it is important to consider that they also increase peripheral vascular resistance. As both blood pressure and EF remained unchanged, we performed a statistical analysis of the collected data.

Studies in adults have shown that reduced EF is generally associated with lower SBP and MBP because these parameters are influenced by cardiac output^{7,8}. In patients with heart failure, a lower EF often correlates significantly with decreased SBP and MBP owing to impaired ventricular function⁹. However,

the relationship between EF and DBP is less consistent because DBP is more dependent on peripheral vascular resistance than on cardiac output¹⁰. In some cases, a markedly low EF has been associated with reduced DBP; however, this relationship has not been uniformly observed across studies. Overall, while EF is a critical indicator of systolic function and influences blood pressure levels, the degree of impact can vary depending on the patient's overall cardiovascular health and the presence of conditions such as heart failure¹¹.

EF can be measured using M-mode echocardiography as the fraction of blood ejected from a ventricle with each heartbeat and serves as a primary indicator of left ventricular systolic function, which can be easily obtained by dividing the volume ejected by the heart (stroke volume) by the volume of the filled heart (end-diastolic volume). Studies in adults have previously

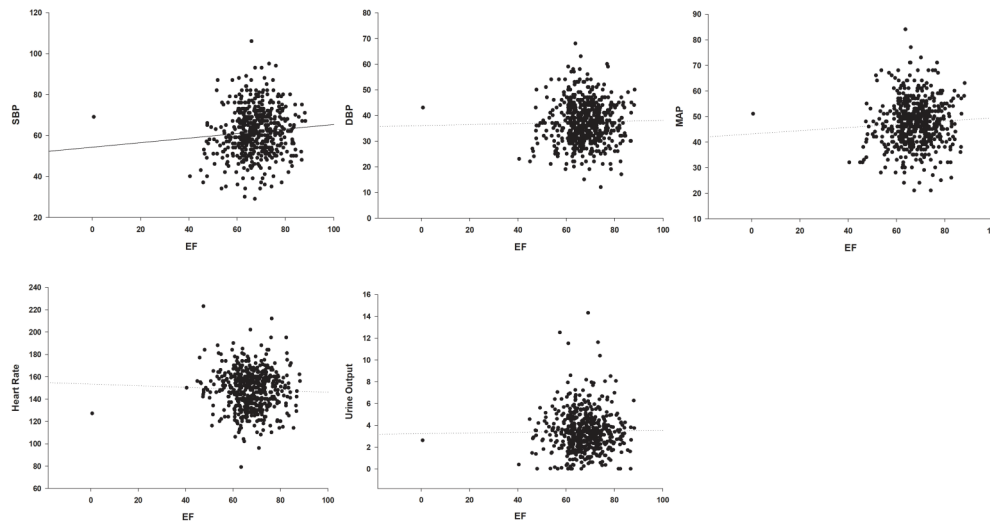


Figure 1. Correlations between ejection fraction (EF) and blood pressure, heart rate, urine output (UO). Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure.

shown that individuals with a low EF showed significantly lower BP than those with a normal EF¹², and that a marked reduction in EF ($\leq 35\%$) is more significantly correlated with hypotension than those with a moderately reduced (35% to 55%) and/or normal-range EF ($\geq 55\%$). Patients diagnosed with congestive heart failure or myocardial infarction demonstrate low cardiac output due to myocardial dysfunction; thus, EF was low in such cases, whereas hypotension was found to be associated in most studies¹²⁻¹⁴. Conversely, our study found no significant correlations between EF and DBP or MBP in neonates, although SBP alone showed a significant correlation with EF ($P=0.046$), which was statistically significant but not clinically meaningful. As shown in Table 3, EF was found to be associated with HR but showed no statistically significant relationship with UO. As shown in Figure 1, EF was weakly correlated with HR and UO. When considering a P -value threshold of <0.001 for significance in multivariate analysis, neither HR nor UO reached statistical significance. These results suggest that the EF is weakly associated with the HR and UO.

Blood pressure depends on the cardiac output and systemic vascular resistance. Cardiac output is determined by the preload, myocardial contractility, and afterload. Some researchers have previously shown that hypotensive preterm infants demonstrate normal or high ventricular output; therefore, their EF may appear to be normal^{15,16}. Preterm infants with hypotension have a limited ability to increase cardiac output in response to volume infusion or the administration of inotropes.

In addition, they are more sensitive to increased afterload, which frequently leads to decreased cardiac output^{17,18}. A previous study reported a weak correlation between left ventricular output and blood pressure in preterm infants¹⁹.

Myocardial dysfunction and abnormal peripheral vasoregulation are the primary causes of hypotension in neonates, including preterm infants. The neonatal myocardium comprises a large quantity of collagen (primarily type I collagen), resulting in a more rigid and less compliant myocardium^{20,21}. Left ventricular relaxation and compliance improve when the collagen content reaches normal levels approximately 1 month after birth²⁰. Myocardial contraction, relaxation and calcium homeostasis in preterm infants differ from those in full-term neonates because immature myocytes rely less on the release and reuptake of calcium from the sarcoplasmic reticulum. Preterm infants also exhibit reduced systolic and diastolic functions and increased sensitivity to increments in afterload, often resulting in decreased cardiac output, consequently causing hypotension in some cases³. Contraction and relaxation of the myocardium are both decreased in preterm infants, indicating that the EF can be normal. Term infants show higher basal contractility than older children, whereas the immature myocardium is more sensitive to changes in afterload; contractility decreases significantly with small increases in afterload. However, following the transitional period, the myocardium tends to adapt to increases in afterload as the blood pressure increases^{2,3}. One study performed in Finland showed

that the diastolic pressure patterns demonstrated by preterm infants represented a transition between those found in the fetus and those in term infants²²⁾. These changes reflect an improvement in left ventricular diastolic function, which is more marked during relaxation than during compliance. Furthermore, in prior studies, age-related changes were observed in diastolic but not systolic heart performance in term infants during the first 6 months of life^{20,22)}.

Neonatal hypotension is associated with several other factors. Our study showed that PDA was significantly associated with low SBP and DBP, consistent with the results of previous studies. Ratner et al.²³⁾ reported that a mean DBP <28 mm Hg on the 3rd day of life was significantly associated with PDA in 93% of patients. Some medications such as fentanyl can also affect blood pressure and are commonly used in infants receiving mechanical ventilation. A previous study reported no statistically significant differences between fentanyl and placebo groups with regard to MBP²⁴⁾. Another study reported that sufentanil and fentanyl had no effect on blood pressure²⁵⁾. However, our study also showed that fentanyl was most significantly correlated with low blood pressure.

A limitation of this study is that it did not compare differences in EF based on inotrope use before versus after cardiac evaluation, as it focused on inotrope use only at the time of cardiac assessment and did not distinguish between the types of inotropes. In addition to myocardial dysfunction, decreased peripheral resistance should also be considered an important factor in the development of neonatal hypotension. Therefore, neonatologists should exercise caution when prescribing medications that can affect the peripheral vascular resistance and potentially lead to hypotension.

ARTICLE INFORMATION

Ethical statement

The study protocol was reviewed and approved by the Institutional Review Board of Chung-Ang University (IRB No. 1708-003-16087). The requirement for informed consent was waived by the Institutional Review Board of Chung-Ang University Hospital because of the retrospective nature of this study.

Conflicts of interest

Na Mi Lee is an editorial board member of the journal, but she was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Author contributions

Conception or design: N.M.L., D.Y.Y., H.K.

Acquisition, analysis, or interpretation of data: N.M.L., D.Y.Y., H.K.

Drafting the work or revising: N.M.L., N.L.Y.

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