Evaluation of left ventricular function parameters in term and preterm neonates at the 1st week of postnatal life

Evaluación de los parámetros de la función ventricular izquierda en recién nacidos a término y prematuros en la 1a semana de vida posnatal

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Abstract

Background The period of time of life where the most dramatic physiologic changes occur is the neonatal period. There are marked physiological alterations that take place during this time, particularly concerning the heart and circulation.

But, the transformation of the fetal into a neonatal circulation in preterm infants is inadequately investigated and the time to choose for comparison between neonates born prematurely and full-term neonates are controversial.

AIMS This study focused on comparison of left ventricular systolic and diastolic function between preterm and term neonates during the postnatal cardiovascular transitional period in the 1st week of life following closure of the major fetal shunts.

Methods Via the use of echocardiography, we evaluated some of the systolic and diastolic parameters of the left ventricular function in 30 preterm neonates at the 1st week of postnatal life and 50 term neonates after closure of the patent ductus arteriosus on 1st the week of postnatal life. Via the use of M-mode ultrasound imaging technique, we measured left ventricular dimensions to estimate fractional shortening FS %. By two dimensional echocardiography 2D ECHO we measured ejection fraction EF% by Simpson's biplane method and left ventricular outflow tract LVOT diameter. Through pulsed-wave Doppler echocardiography, we estimated stroke volume SV and cardiac output CO, and left ventricular diastolic function through measuring the (E and A waves, E/A ratio).

Results We identified a significant difference statistically between the study groups for all variables. Compared with term neonates, preterm infants in the 1st week of life had reduced FS% and EF%, SV and left ventricular CO and reduced transmitral filling indicating some degree of systolic and diastolic function impairment due to insufficient time for extra uterine life physiological adaptations.

Conclusions Preterm neonates at the 1st week of postconceptional age have reduced left ventricular function systolic and diastolic parameters.

Key words left ventricular function, full term, preterm."

Resumen

Antecedentes El período de la vida donde ocurren los cambios fisiológicos más dramáticos es el período neonatal. Hay marcadas alteraciones fisiológicas que se producen durante este tiempo, particularmente en lo que respecta al corazón y la circulación.

Sin embargo, la transformación de la circulación fetal en neonatal en los recién nacidos prematuros no se investiga adecuadamente y el momento de elegir la comparación entre los recién nacidos prematuros y los recién nacidos a término es controvertido.

Objetivos Este estudio se centró en la comparación de la función sistólica y diastólica del ventrículo izquierdo entre recién nacidos prematuros y a término durante el período de transición cardiovascular posnatal en la primera semana de vida después del cierre de las principales derivaciones fetales.

Métodos Mediante el uso de ecocardiografía, evaluamos algunos de los parámetros sistólicos y diastólicos de la función ventricular izquierda en 30 recién nacidos prematuros en la 1ª semana de vida posnatal y 50 recién nacidos a término después del cierre del conducto arterioso persistente en la 1ª semana de vida posnatal. Mediante el uso de la técnica de imágenes de ultrasonido en modo M, medimos las dimensiones del ventrículo izquierdo para estimar el porcentaje de FS de acortamiento fraccional. Mediante ecocardiografía bidimensional, ECHO 2D, medimos la fracción de eyección EF% mediante el método biplano

de Simpson y el diámetro del TSVI del tracto de salida del ventrículo izquierdo. Mediante ecocardiografía Doppler de onda pulsada, estimamos el volumen sistólico VS y el gasto cardíaco CO, y la función diastólica del ventrículo izquierdo midiendo las (ondas E y A, relación E / A).

Resultados Identificamos una diferencia significativa estadísticamente entre los grupos de estudio para todas las variables. En comparación con los recién nacidos a término, los recién nacidos prematuros en la primera semana de vida tenían% de FS y% de FE, SV y GC del ventrículo izquierdo reducidos y un llenado transmitral reducido, lo que indica cierto grado de deterioro de la función sistólica y diastólica debido al tiempo insuficiente para las adaptaciones fisiológicas de la vida extrauterina.

Conclusiones Los recién nacidos prematuros en la 1ª semana de edad posconcepcional tienen parámetros sistólicos y diastólicos de función ventricular izquierda reducidos.

Palabras clave: función ventricular izquierda, término completo, prematuro ".

Introduction

The development of fetal circulation into neonatal form is an intricate process that takes place during the early weeks of life. Following delivery, clamping of the umbilical vessels and the major fetal heart shunts are closed such as the ductus arteriosus, ductus venosus and foramen ovale.

While those alterations allow fetal adaptation to the external environment, they can be quite challenging for the circulatory system[1].

After delivery, there's a change in blood flow; the systemic circulation substitute the circulation in the placenta with an elevation in left ventricular afterload and systemic blood pressure. Moreover, the fetal pulmonary circulation exhibits an increase in the ventricular preload due to changes in flow and resistance[2].

In addition, after the fetal shunts close and the demand for oxygen escalates, the cardiac output nearly doubles post-delivery[3,4], this dramatic fetal to neonatal change in circulation will strain the cardiac tissue of full term babies and to a greater extent those of preterm neonates.

For example, preterm neonates are more susceptible to circulatory failure due to the reduced cardiomyocytes proliferation rate in comparison to the controls[5,6]. Also, preterm neonates usually present with a persistent patent ductus arteriosus PDA that escalates left ventricular LV volume overload and results in left ventricular and subsequently left atrial enlargement and eventually mitral valve insufficiency.

Additionally, when the blood flows from the left to right through persistent ductus arteriosus, the blood flow will increase into the pulmonary circulation and leads to systemic hypotension[7]. In the postnatal circulatory transition period, the prematurely born neonates are at a more risk of developing hemodynamic compromise, what is known regarding LV function is considered little and the possible differences in the function of the heart in this age group during this crucial time. This lack of knowledge is maybe due to the fact of the difficulty in deciding which time is best to perform such compasions[8].

This complex transition is possibly the most intense and pivotal change of human life and while it is thoroughly researched in term infants, this transition is not understood well in preterm. Preterm infants have poorly developed myocardium and some degree of diastolic impairment placing them at an increased risk for cardiac dysfunction. For all the reasons above, it is extremely crucial to clearly understand the physiology of cardiac tissues to direct the management of preterm infants with such circulatory challenges[2].

It is more difficult for preterm infants to shift from fetal to neonatal circulation due to:

incompetent contractility of the immature myocardium that leads to a reduced cardiac performance, persistent shunting across the patent ductus arteriosus is more prevalent in preterm, their ability to raise the heart rate and consequently increase the cardiac output is restricted, the cardiac demands is greater due to the elevated heart rate , and the poorly developed innervation of the immature myocardium may impede the infantile ability to raise the cardiac output and cause it to respond ineffectively in traumatic circumstances[2].

In brief, the mode of transition from foetal to neonatal circulation in preterm infants is complicated, and it can be much more problematic in extremely low-birth-weight babies with hemodynamic instability.[7"]

Methods

The type of this study is a prospective observational/analytic study that was conducted in the neonatal ward at Alkhansaa teaching hospital in Iraq-Mosul city from October 2020 – February 2021.

We included 50 full term neonates who served as the control group and 30 preterm neonates <37 weeks of gestation in the 1st week of postnatal life.

The full-term neonates included in this study were normal and healthy with no underlying disease who were born by normal vaginal delivery or caesarean section. The

preterm neonates incorporated were born prior to their estimated date of delivery before the 37th week of gestation. Any neonate who had a syndrome or a congenital anomaly and those with respiratory complications of prematurity such as respiratory distress syndrome that may require ventilation, sepsis, and PDA. Neonates with maternal disease that might have a potential impact on myocardial function such as diabetes were also excluded. The children were examined by a stethoscope to detect the presence of a murmur in the heart and was found to be normal on clinical examination. The study was approved by the scientific committee of the medical college of Mosul university. For all of the neonates included in the study a written consent from the parents or the caregiver was obtained."

- Baseline clinical characteristics: Were obtained which comprised the following: The age (in weeks), The recumbent length (in cm) and body weight in (kg) using a infantometer and mechanical weight scale were measured for each baby at the time of the general physical examination, and those values were used to calculate body surface area BSA via the use of using the DuBois formula as the following equation:'BSA (m2) = (0.0001) (71.84) (Wt0.425) (Ht0.725)[10], mode of delivery and oxygen saturation SPO2%.

- Echocardiography analysis: With the patient lying supine. Transthoracic echocardiographic examination was performed. Sedation was not required during echocardiographic examination two- dimensional, M-mode and Doppler echocardiographic examination were performed by a Pediatric cardiologist-echo cardiographer according to ASE/EAE/ AEPC guidelines[11] using (Philips Effiniti 30 machine, with 10 MHz transducer). All images were recorded in the echocardiography machine for further offline measurement and analysis.

  - M-mode echocardiography: With subjects resting in supine position, a preliminary two dimension study in the parasternal long axis PLAX and short axis view to evaluate cardiac structures and obtain visual assessment of LV contractile function was performed. M-mode study was done at the level of mitral valve leaflet tips with M-mode line in the parasternal long axis view to measure: left ventricular internal dimension at diastole (LVIDd) and left ventricular internal dimension at systole (LVIDs). From which, the ECHO device will generate FS by the following formula: - FS (LVIDd – LVIDs)/ (LVIDd) ×100[12]
  - 2D echocardiography: We determined the diameter of the left ventricular outflow tract (LVOT) at the parasternal long-axis view from an inner edge to an inner edge in mid-systole and calculated the cross-sectional area at the LVOT by the following formula: _ ϖ D2/4 where ϖ is the constant 3.14 and D is the diameter of the vessel. We also estimated ejection fraction EF by Simpson's biplane method.[12]
  - Pulsed wave Doppler: Using pulsed wave Doppler echocardiography at the apical 5 chamber view by placing the pulsed wave PW Doppler cursor at the level of LVOT to obtain the velocity profile through tracing of the spectral Doppler envelope to determine the LVOT Velocity time integral VTI. Transmitral velocity was also obtained to calculate the E wave, A wave and E/A ratio as an indicator of diastolic heart function.[12]

- Statistical analysis: All of the data were analyzed utilizing the Statistical Package for Social Science (SPSS) software version 25 and these were expressed as mean ± standard deviation.[13] Descriptive analysis of the data was also done using frequency distribution and histogram graphs, to describe some of the parameters in the study.

Unpaired independent t-test was used to compare between term & preterm study population for some of the parameters in the study.

Results

Table (1) Comparing term neonates with preterm neonates, there were significant differences in the gestational age of 38.62±1.14 in term and 34.37±1.586 in preterm neonates, weight of 3.222±0.213 in term and 1.713±0.289 in preterm neonates. In the preterm neonates heart rate was significantly higher of 147.400±2.457. While SPO2% was not higher in term neonates than preterm neonates as shown in table 1

Table 1 - Comparison of baseline clinical characteristics between term and preterm neonates.

Parameter	Term	Preterm
Gestational age at birth/weeks (Means ± SD)	38.62 ± 1.14	34.37 ± 1.586
Sex Male/Female (Frequency of Number)	35 / 15	17 / 13
Weight/Kg (Means ± SD), P Value	3.222 ± 0.213	1.713 ± 0.289
	(t = 24.779) P- value = 0.000**	
Height/Cm (Means ± SD), P Value	49.000 ± 1.195	38.800 ± 1.954
	(t = 25.831) P- value = 0.000**	
BSA/Cm2 (Means ± SD), P Value	0.209 ± 0.007	0.135 ± 0.014
	(t = 26.132) P- value = 0.000**	
Mode of delivery /C.S or NVD. N (%)	CS = 21, NVD = 29	CS = 15, NVD = 15
Heart rate beat/min (Means ± SD), P Value	138.040 ± 4.081	147.400 ± 2.457
	(t = 12.804) P- value = 0.000**	
SPO2% (Means ± SD), P Value	97.520 ± 1.249	97.067 ± 1.112
	(t = 1.684) P- value = 0.097	

** Highly Significant at p ≤ 0.01

Table (2) Summarizes the systolic parameters data for preterm infants obtained at the 1st week post-delivery, in comparison with age-matched term controls. Significant differences in LV shortening and ejection fraction were observed between preterm infants and term neonates. With significantly higher FS % of 35.820±2.455 and EF% of 71.820±4.345 in term neonates.

Table 2 – Comparison of fractional shortening and ejection fraction by Simpson's biplane method in term vs. preterm neonates.

Parameter	Term	Preterm
Fractional Shortening FS % (Means ± SD), P Value	35.820 ± 2.455	33.933 ± 2.180
	(t = 3.572) P- value = 0.001**	
Ejection Fraction by Simpson's biplane method EF% (Means ± SD), P Value	71.820 ± 4.345	68.800 ± 3.898

** Highly Significant at p ≤ 0.01

Table (3) shows that term neonates, compared to preterm neonates regarding left ventricular hemodynamics, were associated with higher stroke volume of 1.940±0.141 in term and 1.598±0.111 in preterm neonates, cardiac output of 267.713±18.301 and 235.523±15.045 in term and preterm neonates respectively.

Table 3- Comparison of left ventricular hemodynamic parameters, stroke volume (ml/kg) cardiac output (ml/min/kg) between the study groups.

Parameter	Term	Preterm
1.Stroke volume ml/kg (Means ± SD), P Value	1.940 ± 0.141	1.598 ± 0.111
	(t = 11.986) P- value = 0.000**	
2.Cardiac output ml/min/kg (Means ± SD), P Value	267.713 ± 18.301	235.523 ± 15.045
	(t = 8.529) P- value = 0.000**	
	(t = 16.469) P- value = 0.000**	

** Highly Significant at p ≤ 0.01

Table (4), significant differences in mitral flow velocities were observed between term and preterm neonates. A significantly higher E velocity of 59.660±5.615 and A velocity of 49.560±6.051 with significantly higher E/A ratio of 1.210±0.084 were observed in the term neonates compared to preterm neonates.

Table 4- The transmittal flow velocity difference between the study groups.

Parameter	Term	Preterm
E-Wave Cm/sec (Means ± SD), P Value	59.660 ± 5.615	39.600 ± 4.383
	(t = 17.792) P- value = 0.000**	
A-Wave Cm/sec (Means ± SD), P Value	49.560 ± 6.051	47.300 ± 4.300
	(t = 1.946) P- value = 0.050*	
E/A ratio (Means ± SD), P Value	1.210 ± 0.084	0.838 ± 0.067
	(t = 21.624) P- value = 0.000**	

* Normal Significant at p ≤ 0.05

** Highly Significant at p ≤ 0.01

Discussion

The evaluation of neonatal hemodynamics is very complex, and it should include more than just measuring blood pressure, heart rate, and other clinical variables. Neonatologist-performed echocardiography has the ability to detect cardiovascular failure early, to implement of a customized treatment plan, and to monitor therapeutic outcomes[14].

In this study after PDA closure and during the first week of life, preterm neonates had lower FS% and EF% by Simpson's biplane method, both of which are measures of systolic activity of the heart.

We presume that the lower values of FS% and EF% in preterm neonates obtained in our data is due to the fact of a smaller myocardium in preterm neonates. Since the M-mode echocardiographic imaging reflect the movement of the anterior and posterior LV walls more than that of the anterior wall; therefore, FS% and EF% may undervalue LV systolic function in these infants[8].

Similarly, in another study conducted by Kozak-Barany et al. preterm neonates had a significantly low FS% at 1 month of postnatal life and presumed that the underlying cause is a decreased expression of contractile proteins in heart sarcomeres in preterm neonates[15].

In the current study, term neonates had significantly higher stroke volume SV and left ventricular cardiac output LVO CO (which was proportional to SV changes) than preterm neonates. This may be clarified by preterm neonates having a less mature and complaint myocardium. The foetal myocardium produces less active stress than the more mature myocardium in isolated myocardial fiber tests, which may be due to the immature heart's lower proportion of contractile components, shorter and less coordinated myofibrils[16], decreased calcium handling capacity[17,18].

Since the autonomic nervous system through its sympathetic and parasympathetic subdivisions are in charge of controlling the heart rate. Newborns have a rapid heart rate, which is associated with cardiac-related sympathetic predominance and reduced vagal activity. On the basis of previous studies[19], it was believed that changes in heart rate, rather than changes in stroke volume, affect cardiac production in neonates and infants. In recent years, evidence has been provided that human neonates and infants may have a greater capacity to change stroke volume than previously thought[20].

The ventricles fill most in atrial systole in the fetus and preterm neonates, however as gestation progresses, the filling velocities and velocity-time integrals during early diastole gradually increase, leading more to ventricular filling[20]. These improvements are thought to be due to the fetal myocardium relaxing and complying more[20].

These changes, which are noticed soon after delivery and with no evident worsening overtime, might indicate that these noticed findings are associated more to maturation process than pathological changes. Myocardial relaxation needs an uptake of calcium ions; however, the immature myocardium has less mature sarcoplasmic reticulum, differences in functional handling of calcium, and a less number of calcium channel pumps, all of the above could be a contributing factors to less powerful relaxation of the myocardium[21].

Such variations, which appear shortly after delivery and do not appear to escalate over time, may indicate that the observed differences are due to maturational rather than pathologic changes.

Calcium absorption is needed for myocardial relaxation; however, a less evolved sarcoplasmic reticulum is present in the underdeveloped myocardium, functional variations in calcium handling, and decreased calcium channel pumps, all of which can lead to less proficient relaxation[18,21,22].

Aside from developmental variations, defects in diastolic function may be the result of pathologic changes in the immature myocardium as a result of early exposure to the burdens of the postnatal circulation[22].

Previous pulsed Doppler investigations of preterm infants studied serially in early infancy corroborate this finding. When compared to age-matched controls, Harada et al. discovered" discrepancy in LV function of 18 preterm infants born at (26–32 weeks) at a median of 14 days and a follow-up median of 94 days, including lower pulsed Doppler LV E velocities and E/A ratios, as well as lower A-wave velocities.

Also at 3 to 6 months of age, Schmitz et al. found that preterm infants' LV filling was changed[23,24].

Preterm neonates had lower diastolic function (E/A ratio) according to Hirose et al; however, these researchers looked at preterm neonates 4 weeks after birth, while Bokiniec et al monitored preterm neonates after 14 to 18 weeks of postnatal life (ie, allowing adequate time for postnatal alteration of diastolic heart function). Indeed, a previous study found that in the first month of life, preterm neonates' LV diastolic function improved to normal levels[25,8].

It's unclear if these variations in diastolic function will ever go away or will continue to lead to myocardial anomalies in function and structure in affected adults, such as decreased relaxation[25].

In preterm infants, altered diastolic function properties of the myocardium are likely to affect ventricular loading and thus cardiac output. The ventricle requires enough time to fill in diastole to achieve adequate preload needed to maintain normal stroke volume and production in myocardial disease states associated with diastolic dysfunction[26].

While tachycardia may be harmful to preterm infants since it may decrease ventricular filling time if the preterm myocardium is unable to relax. Inotropes with b-sympathomimetic effects that cause tachycardia can be ineffective unless they also have a lusitropic effect.

Increased preload, which can be assisted by the volume administration, as well as the use of other agents to promote systemic circulation without changing heart rate, can result in a faster increase in cardiac output. Recent research in isolated preterm piglet hearts suggests that the preterm heart could have a stronger "preload reserve," and that increasing preload is the best way to increase cardiac output[27]. Further clinical researches are required to establish the limitations of the underdeveloped myocardium's diastolic capability and the best approach to boost cardiac performance in the preterm heart."

Conclusions

The apparently well and stable preterm neonates assessed by echocardiography at the 1st 7th days of postnatal life have altered LV systolic and diastolic function parameters when compared to the full term neonates of the same postnatal age that may relate to a great extent to developmental and maturation impact and diminished transmitral early filling. Our study findings suggest preterm infants start life with an underdeveloped myocardium affecting both systolic and diastolic parameters of the left ventricle of the neonate."

References

1. Morton SU, Brodsky D. Fetal physiology and the transition to extrauterine life. Clin Perinatol. 2016; 43:395-407.
2. Singh Y, Tissot C. Echocardiographic evaluation of transitional circulation for the neonatologists. Front Pediatr. 2018; 6:140.
3. Hillman NH, Kallapur SG, Jobe AH. Physiology of transition from intrauterine to extrauterine life. Clin Perinatol. 2012; 39:769-783.
4. Assessment of cardiac hemodynamic changes during pregnancy in normal and hypertensive women. Annals of the College of Medicine, Mosul, 2018; 40(2):9-17. doi:10.33899/med.2018.160007
5. Bensley JG, Moore L, De Matteo R, et al. Impact of preterm birth on the developing myocardium of the neonate. Pediatr Res. 2018; 83:880-888.
6. Dice JE, Bhatia J. Patent ductus arteriosus: an overview. J Pediatr Pharmacol Ther. 2007; 12:138-146.
7. Mathew B, Lakshminrusimha S. Persistent pulmonary hypertension in the newborn. Children (Basel). 2017; 4:63.
8. Bokiniec R, Własienko P, Szymkiewicz-Dangel J, Borszewska-Kornacka MK. Echocardiographic analysis of left ventricular function in term and preterm neonates at week 40 of postconceptional life. Kardiol

Pol. 2019 Jan 13;77(4):445-450. doi: 10.5603/KP.a2019.0040. Epub 2019 Feb 27. PMID: 30835331.

9. Noori S, Friedlich P, Wong P, et al. Hemodynamic changes after low-dosage hydrocortisone administration in vasopressor treated preterm and term neonates. Pediatrics. 2006; 118:1456-1466.

10. Du Bois, D. & Du Bois, E. F. A formula to estimate the approximate surface area if height and weight be known. Nutrition, 5(5):303-11, 1989.

11. Luc Mertens, Istvan Seri, Jan Marek, Romaine Arlettaz,et al. Targeted Neonatal Echocardiography in the Neonatal Intensive Care Unit: Practice Guidelines and Recommendations for Training, European Journal of Echocardiography, Volume 12, Issue 10, October 2011, Pages 715–736,

12. Siassi B., Noori S., Acherman R., Wong P. Practical Neonatal Echocardiography 1st ed. MC Graw Hill Education. 2019; p78,79,80,121,22,23.

13. Barton B and Peat J. Medical Statistics: A Guide to SPSS, Data analysis and Critical Appraisal. 2nd ed. Wiley Blackwell. 2014.

14. de Boode, W.P., van der Lee, R., Horsberg Eriksen, B. et al. The role of Neonatologist Performed Echocardiography in the assessment and management of neonatal shock. Pediatr Res 84,57–67 (2018). https://doi.org/10.1038/s41390-018-0081-1).

15. Kozák-Bárány A, Jokinen E, Saraste M, et al. Development of left ventricular systolic and diastolic function in preterm infants during the first month of life: a prospective follow-up study. J Pediatr. 2001; 139: 539-545.

16. Anderson PA. The heart and development. Semin Perinatol 1996;20:482-509.

17. Kaufman TM, Horton JW, White DJ, Mahony L. Age-related changes in myocardial relaxation and sarcoplasmic reticulum function. Am J Physiol 1990;259:H309-16.

18. Mahony L. Regulation of intracellular calcium concentration in the developing heart. Cardiovasc Res 1996;31(Spec No):E61-7.

19. Lebowitz EA, Novick JS, Rudolph AM. Development of myocardial sympathetic innervation in the fetal lamb. Pediatr Res 1972: 6:887–893

20. Gullberg N, Winberg P, Selldén H. Changes in stroke volume cause change in cardiac output in neonates and infants when mean airway pressure is altered. Acta Anaesthesiol Scand. 1999 Nov;43(10):999-1004. doi: 10.1034/j.1399-6576.1999.431005.x. PMID: 10593461.)

21. Mahony L. Calcium homeostasis and control of contractility in the developing heart. Semin Perinatol 1996;20:510-9.

22. Kaufman TM, Horton JW, White DJ, Mahony L. Age-related changes in myocardial relaxation and sarcoplasmic reticulum function. Am J Physiol 1990;259:H309-16.

23. Harada K, Ogawa M, Tanaka T. Right ventricular pre-ejection myocardial velocity and myocardial acceleration in normal fetuses assessed by Doppler tissue imaging. J Am Soc Echocardiogr 2005;18:370-4.

24. Schmitz L, Stiller B, Pees C, Koch H, Xanthopoulos A, Lange P. Doppler-derived parameters of diastolic left ventricular function in preterm infants with a birth weight <1500 g: reference values and differences to term infants. Early Hum Dev 2004;76:101-14.

25. Hirose A, Khoo NS, Aziz K, Al-Rajaa N, van den Boom J, Savard W, Brooks P, Hornberger LK. Evolution of left ventricular function in the preterm infant. J Am Soc Echocardiogr. 2015 Mar;28(3):302-8. doi: 10.1016/j.echo.2014.10.017. Epub 2014 Dec 18. PMID: 25533193.

26. Wachter R, Schmidt-Schweda S, Westermann D, Post H, Edelmann F, Kasner M, et al. Blunted frequency-dependent upregulation of cardiac output is related to impaired relaxation in diastolic heart failure. Eur Heart J 2009;30:3027-36.

27. Eiby YA, Lumbers ER, Headrick JP, Lingwood BE. Left ventricular output and aortic blood flow in response to changes in preload and afterload in the preterm piglet heart. Am J Physiol Regulat Integrat Compar Physiol 2012;303:R769-77.