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Diastolic function in neonates after the arterial switch operation: effects of positive pressure ventilation and inspiratory time

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Abstract *Objective*: To determine the effects positive pressure ventilation have on left ventricular diastolic function in neonates after the arterial switch operation.
Design: Prospective case series.
Setting: Pediatric cardiac and multidisciplinary intensive care units in two university-affiliated children's hospitals.
Patients and participants: The patient population consisted of 12 neonates weighing 2.5–4.2 kg with D-transposition of the great arteries (DTGA) who underwent arterial switch operation.
Interventions: All patients were mechanically ventilated in a volume-targeted mode with a square wave flow pattern. The positive end-expiratory pressure was held constant. A long inspiratory time was set by extending it over three cardiac cycles.
Measurements and results: Pulsed Doppler measurements of left ventricular diastolic function were performed during the following cardiac cycles: (1) the last diastolic period of expiration (E_L), (2) first, second and third diastolic periods of inspiration (I_1, I_2, I_3) and (3) the first diastolic period of expiration (E_F). Doppler measurements of peak E wave, peak A wave, E area/A area, E area fraction, A area fraction, 0.33 area fraction and the deceleration time were made. Doppler tracings were digitized and the data obtained from three sequential study periods were averaged. Data were statistically analyzed using the repeated measures analysis of variance procedure. During (I_1), there was a 21 % increase in the peak E wave (0.53 ± 0.06 vs 0.64 ± 0.08 m/s, p < 0.01) and 28 % increase in peak A wave (0.47 ± 0.07 vs 0.60 ± 0.08 m/s, $p < 0.01$) compared to (E_L). There was a 24 % increase in total area under the E and A waves when I_1 was compared to E_L (0.059 ± 0.008 vs 0.073 ± 0.009, $p < 0.01$) and there was no change in mitral valve deceleration time. Compared to the initial diastolic period during inspiration (I_1), the third diastolic period during inspiration (I_3) had a 38 % decrease in peak E (0.64 ± 0.08 vs 0.40 ± 0.05 m/s, $p < 0.01$) and 33 % decrease in peak A (0.60 ± 0.09 vs 0.40 ± 0.05 m/s, $p < 0.01$). In addition, there was a 16 % reduction in total area under the E and A waves (0.073 ± 0.009 vs 0.061 ± 0.008, $p < 0.01$). There were no changes in the other diastolic indexes that reflect changes in ventricular compliance or relaxation.
Conclusions: In neonates with transposition of the great arteries (TGA) after the arterial switch operation, positive pressure ventilation augments left ventricular filling during the early phase of inspiration. Prolonging the inspiratory time over three cardiac cycles results in a reduction in left ventricular filling during the third diastolic period.

There were no changes in the other diastolic indexes that reflect changes in ventricular compliance or relaxation.

Key words Cardiopulmonary interactions · Congenital heart disease · D-transposition of the great arteries · Diastolic function · Doppler ultrasonography · Inspiratory time

Introduction

After the arterial switch operation, neonates are at high risk for developing left ventricular dysfunction [1, 2, 3, 4, 5, 6] due to cardiopulmonary bypass, period of deep hypothermic circulatory arrest and coronary artery reimplantation. Pharmacological approaches have been developed to improve left ventricular systolic function [6]. In addition, newer strategies for mechanical ventilation combined with advances in ventilator technology have been used to assist cardiac function in children [7, 8, 9] and adults [10, 11, 12].

Assessment of diastolic function using Doppler ultrasound techniques was initially studied in adults and correlated to invasive hemodynamic and nuclear angiographic studies [13, 14, 15]. In recent years, Doppler echocardiography has been used to measure diastolic function in normal neonates and children and detect abnormalities in those with cardiac disorders [16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26]. Previous studies have examined the effect normal tidal breathing has on the diastolic indexes in children [23]. An additional study examined the effects of positive pressure ventilation on diastolic filling in premature infants [24]. Abnormalities in diastolic function in the immediate postoperative period have been correlated with increased morbidity and mortality in neonates and children after cardiac surgery [25, 26]. For these reasons, understanding abnormalities in diastolic function and developing strategies for treating diastolic dysfunction in intubated, mechanically ventilated neonates with congenital heart disease in the immediate postoperative period is of utmost importance.

The purpose of this investigation was to determine the effect positive pressure ventilation, in particular, a prolonged inspiratory time, has on left ventricular diastolic function in intubated neonates after the arterial switch operation.

Materials and methods

Patients

The patient population consisted of 12 neonates weighing 2.5–4.2 kg with DTGA with intact ventricular septum who underwent the arterial switch operation before 3 weeks of age (median age = 5 days). Patients were stabilized in the pediatric intensive care unit for 12–24 h and were paralyzed prior to initiation of the single study period. No alterations in inotropic agents or fluid administration were made during the study period. There were no changes in the patient's hemodynamic status during the study period. This study was approved by the Institutional Review Board and informed consent was obtained.

Echocardiographic examination

A two-dimensional echocardiographic examination was performed to exclude the presence of residual intracardiac shunting, mitral regurgitation, left ventricular outflow tract obstruction and qualitatively abnormal systolic function, using a 128 element 5 or 7 MHz phased linear array transducer (Acuson, Mountainview, Calif.). Pulsed Doppler examinations of the left ventricular inflow were obtained using the apical four chamber view. The Doppler sample volume was placed in the mitral valve funnel at an angle as parallel to flow as possible. The sample volume position was adjusted so as to record maximal velocities through the mitral valve (usually at the tips of the leaflets). A respirometer was placed inline with the ventilator and the respiratory cycles were recorded simultaneously with the Doppler tracing. All Doppler examinations were recorded at a paper speed of 100 mm/s. The Doppler areas were traced from the paper recordings using a digitizing tablet with a crosswire cursor, a personal computer and commercially available computer software (Freeland Medical Systems). The Doppler velocities and areas were measured by tracing the outermost border of the spectral recordings.

From the mitral valve Doppler tracing, several indexes of ventricular diastolic function were measured using standard techniques [13, 17] (Fig. 1). Specifically, the peak velocity during rapid ventricular filling, the peak E velocity, the peak velocity during atrial contraction, the peak A velocity and the ratio of the peak E to peak A velocities (E/A ratio) were measured to describe the pattern of ventricular diastolic filling. The deceleration time was measured from the time of peak E to baseline. In addition, the following Doppler areas were measured: the Doppler area in the first third of diastole (0.33 area), during early diastolic inflow (E area), during atrial contraction (A area) and total area under the Doppler curve. The area fractions were calculated by dividing the individual areas by the total area under the Doppler curve. Standard techniques were used to determine area velocities when separate E and A waves were not present [16]. Samples were chosen for analysis when inspiration occurred over three complete cardiac cycles (Fig. 2).

Pulsed Doppler measurements of left ventricular filling were calculated for the following diastolic periods: the last diastolic period of expiration prior to inspiration (E_L), first, second and third diastolic periods of inspiration (I_1, I_2, I_3) and the first diastolic period of expiration (E_F) (Fig. 2).

Mechanical ventilation

Patients were placed in a volume-targeted mode of ventilation with a square flow pattern (Siemens 900 C, Siemens Elma, Stock-

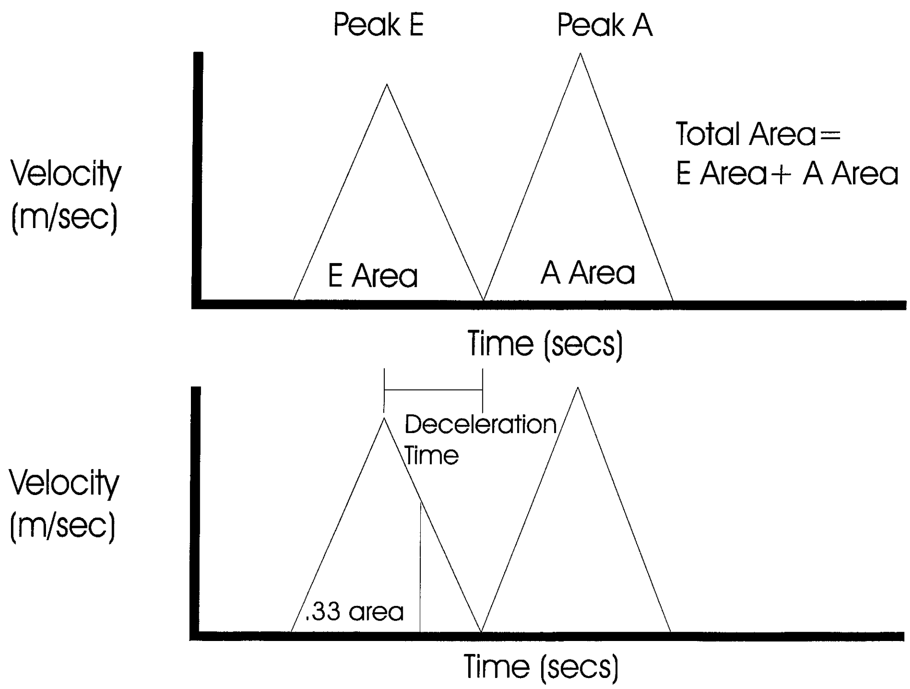

Fig. 1 Schematic representation of left ventricular Doppler filling patterns. The E wave occurs during the passive filling period while the A wave occurs during atrial contraction. The peak E and A waves and areas under the E and A waves are shown

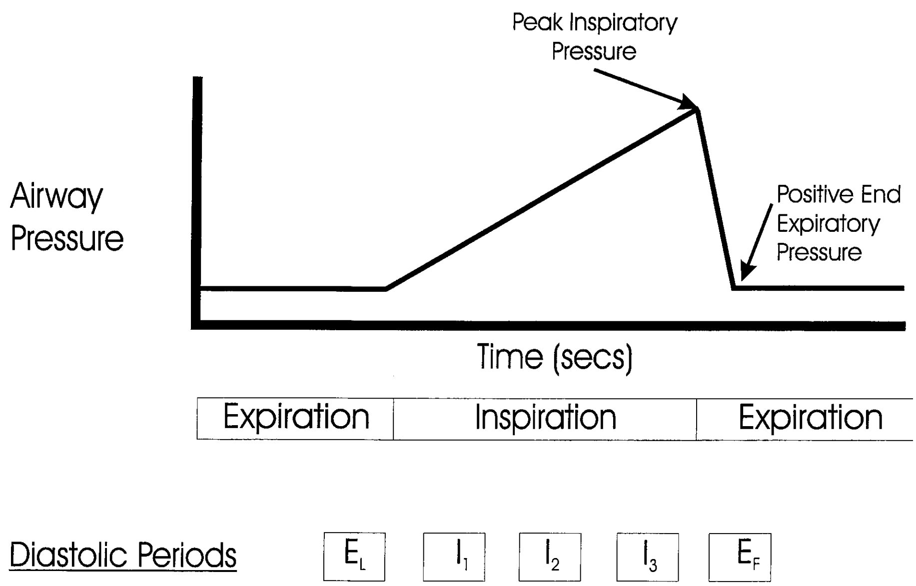

Fig. 2 Schematic representation of the experimental protocol. Inspiration and expiration are shown below a representation of the airway pressures generated by the ventilator. Measurements of diastolic filling were made during the following: last expiratory diastolic period (E_L), during the first three inspiratory diastolic periods (I_1), (I_2), (I_3) and the first expiratory diastolic period (E_F) after inspiration

holm, Sweden). The tidal volume was set at 10 ml/kg (delivered) resulting in peak inspiratory pressures of 30 ± 2 cmH_20 and mean airway pressures of 11 ± 3 cmH_20. The ventilator rate was set at 25 ± 5 breaths/min. The positive end-expiratory pressure was held constant at 4 ± 2 cmH_20. The inspiratory time was adjusted to occur over three cardiac cycles (1.2 ± 0.1 s).

Statistical analyses

Three cardiac cycles were measured and averaged to obtain each individual data point. Statistical comparisons between cardiac cycles were made using the repeated measures analysis of variance procedure. All values are reported as mean ± standard deviation.

Results

The data are summarized in Table 1. The heart rate, blood pressure and right atrial filling pressures remained constant throughout the study periods.

Table 1 Doppler parameters of diastolic filling (*bpm* beats per min, E_L last diastolic period prior to inspiration, E_F first diastolic period after inspiration, I_1 first diastolic period of inspiration, I_2 second diastolic period of inspiration, I_3 third diastolic period of inspiration, *m* meters, *s* seconds)

	Peak E (m/sec)	Peak A (m/sec)	Peak E/A	Total area (m)	E/Total area	A/Total area	0.3/Total area	E/A area	Deceleration time (sec)	Heart rate (bpm)
E_L	0.53 ± 0.06	0.47 ± 0.07	1.07 ± 0.07	0.059 ± 0.008	0.73 ± 0.02	0.55 ± 0.05	0.30 ± 0.14	1.44 ± 0.14	0.045 ± .006	158 ± 7
I_1	0.64 ± 0.08[a]	0.60 ± 0.08[a]	1.04 ± 0.06	0.073 ± 0.009[a]	0.73 ± 0.03	0.59 ± 0.06	0.29 ± 0.13	1.32 ± 0.13	0.046 ± .006	157 ± 6
I_2	0.55 ± 0.05	0.51 ± 0.05	1.19 ± 0.08	0.064 ± 0.008	0.71 ± 0.03	0.51 ± 0.06	0.31 ± 0.14	1.56 ± 0.16	0.049 ± .005	156 ± 8
I_3	0.40 ± 0.05[b]	0.40 ± 0.05[b]	1.01 ± 0.06	0.061 ± 0.008[b]	0.68 ± 0.02	0.56 ± 0.05	0.31 ± 0.15	1.26 ± 0.15	0.050 ± .008	157 ± 6
E_F	0.36 ± 0.04[c]	0.36 ± 0.04[c]	1.02 ± 0.07	0.049 ± 0.006[c]	0.71 ± 0.03	0.54 ± 0.05	0.30 ± 0.13	1.33 ± 0.14	0.049 ± .005	157 ± 7

[a] $p < 0.05$ E_L vs I_1
[b] $p < 0.05$ I_1 vs I_3
[c] $p < 0.05$ I_1 vs E_F

Last expiratory diastolic period (E_L)versus initial inspiratory diastolic period (I_1)

There was a 21% increase in the mitral valve peak E wave (0.53 ± 0.06 vs 0.64 ± 0.08 m/s, $p < 0.01$) and a 28% increase in peak A wave (0.47 ± 0.07 vs 0.60 ± 0.08 m/s, $p < 0.01$) during the first diastolic period of inspiration (I_1) when compared to the last diastolic period of expiration (E_L) (Table 1). There was also a 24% increase in total area under the Doppler curve when comparing the same time periods (0.059 ± 0.008 vs 0.073 ± 0.009, $p < 0.01$) (Table 1). There were no changes in mitral valve deceleration time, E/A ratio or area fractions (Table 1).

Initial inspiratory diastolic period (I_1) versus subsequent inspiratory diastolic periods(I_2,I_3)

Left ventricular filling during late inspiration (I_3) was decreased when compared to early inspiration (I_1). There was a 38% decrease in mitral valve peak E (0.64 ± 0.08 vs 0.40 ± 0.05 m/s, $p < 0.01$) and a 33% decrease in peak A (0.60 ± 0.09 vs 0.40 ± 0.05 m/s, $p < 0.01$) when comparing these two diastolic periods (Table 1). In addition, there was a 16% reduction in total area, (0.073 ± 0.009 vs 0.061 ± 0.008, $p < 0.01$) (Table 1). There were no significant changes in the deceleration time, E/A ratio or area fractions (Table 1). There were no significant changes in any diastolic parameter when comparing I_1 to I_2 or I_2 to I_3.

Initial inspiratory diastolic period (I_1) versus first expiratory diastolic period (E_F)

When comparing the first diastolic period of inspiration (I_1) to the first diastolic period of expiration (E_F), there was a 44% decrease in mitral valve peak E (0.64 ± 0.08 vs 0.36 ± 0.04 m/s, $p < 0.01$) and a 40% decrease in peak A (0.60 ± 0.08 vs 0.36 ± 0.04 m/s, $p < 0.01$) (Table 1). There was also a 31% reduction in total area when I_1 was compared to E_F (0.073 ± 0.009 vs 0.049 ± 0.006) (Table 1). There were no changes in the deceleration time, E/A ratios or area fractions (Table 1).

Last (E_L) and first (E_F) expiratory diastolic periods

The last diastolic period of expiration (E_L) *prior* to inspiration was then compared to the first expiratory diastolic period *after* inspiration (E_F) in order to compare the delayed effects of inspiration. There was a significant reduction in left ventricular filling during the first (E_F) expiratory diastolic period *after* inspiration. Specifically, there was a 32% decrease in mitral valve peak E (0.53 ± 0.06 vs 0.36 ± 0.04 m/s, $p < 0.01$) and a 23% decrease in peak A (0.47 ± 0.07 vs 0.36 ± 0.04 m/s, $p < 0.01$) when E_F was compared to E_L (Table 1). There was a 16% reduction in total area (0.059 ± 0.008 vs 0.049 ± 0.006) but no significant difference in the deceleration time, E/A ratio or area fractions (Table 1).

Discussion

The neonatal myocardium differs significantly from the adult myocardium in its intrinsic structure and function, leading to decreased relaxation and compliance [22, 27]. The decrease in ventricular compliance may in part be due to the decreased number of contractile elements found in neonatal myocardium [27]. Several Doppler-derived indexes have been developed in adults and applied in children to measure diastolic function [16]. The newborn's indexes of left ventricular diastolic function compared to normal adults reveal: decreased peak E wave, peak E/A ratio, E / A area, E area / total area and 0.33 area fraction; prolonged isovolemic relaxation time and deceleration time and no change in the peak A wave and A area / total area [22]. These indexes are influenced by heart rate, preload, afterload, age and phase of respiratory cycle [16, 23].

Abnormalities of diastolic function have important implications for critically ill neonates and children after repair of complex cardiac lesions. Cullen et al. found that mechanically ventilating children following repair of tetralogy of Fallot with restrictive diastolic physiology results in prolonged ICU and hospital stays [25]. Li et al. [26] found that mid diastolic flow reversal on the mitral valve Doppler inflow in neonates after repair of complex cardiac defects leads to increased ICU and hospital stays with a greatly increased mortality (33%). Therefore, understanding and improving diastolic function in these neonates and children has the potential for reducing both morbidity and mortality.

Patients with DTGA were the subjects of interest in this study since they represent a group of relatively homogenous patients who undergo cardiopulmonary bypass with deep hypothermic circulatory arrest and coronary transfer resulting in myocardial injury and dysfunction. It is likely that they would benefit most from understanding and improving diastolic function, as would other patient groups, such as those with cardiomyopathy/myocarditis or left ventricular outflow track obstruction.

Positive pressure ventilation primarily affects cardiac output by increasing intrathoracic pressure and altering lung volume, which results in changes in ventricular preload and afterload [22, 23, 24, 28, 29, 30]. While alterations in heart rate and intrinsic contractility may occur, their roles are minor. The thoracic pump mechanism explains a phasic increase in intrathoracic pressure which increases cardiac output by augmenting left ventricular preload and decreasing left ventricular afterload [31, 32]. These complex cardiopulmonary interactions constantly affect mechanically ventilated neonates after repair of complex congenital heart disease.

Extrapolation from our data would suggest that using positive pressure ventilation with a short inspiratory time will prevent the decrease in left ventricular filling that occurs after a long inspiration and, therefore, maximize cardiac output. The increase in peak E, peak A wave and total area under the Doppler curve indicates that there is an increase in total left ventricular filling during early inspiration. The lack of change in area fractions, E/A velocity ratio and deceleration time suggests that no significant changes occurred in the measures of left ventricular relaxation or compliance. As the duration of inspiration lengthens, a decrease in left ventricular filling occurs. A significant reduction in left ventricular filling, as evidenced by the decrease in the Doppler flow velocities, occurs by the third diastolic period after inspiration has begun. This reduction in left ventricular filling is multifactorial. When intrathoracic pressure increases, systemic venous return, right atrial volume and right ventricular volume decrease, and right ventricular output falls. In response to the decrease in right ventricular output, left ventricular filling falls dramatically during late inspiration and reaches a nadir during the first diastolic period of expiration (E_F). While these effects are occurring, left ventricular afterload is simultaneously decreased by the rise in intrathoracic pressure, causing a decrease in left ventricular transmural pressure. Cardiac output is the net result of these complex cardiopulmonary interactions [28, 29, 30].

One important negative finding revealed in this study was that, in the early postoperative period after repair of TGA, ventricular compliance and relaxation were not affected by prolonged increases in intrathoracic pressure. We had hypothesized that this might have occurred due to a more favorable septal position induced by a decrease in right ventricular preload [33] with a simultaneous decrease in left ventricular afterload. While we were unable to demonstrate this with our pulsed Doppler techniques, newer methods using Doppler tissue imaging may be more sensitive.

The limitations of this study include the following: changes that occur in left ventricular filling with prolonged inspiration may not necessarily result in a change in stroke volume or cardiac output since this could not be simultaneously measured with ultrasonography. In addition, this study did not compare normal intubated neonates to neonates after repair of DTGA nor evaluate those neonates before operation. This would have been helpful in separating the effects of surgery from the diastolic dysfunction that already exists in all neonates.

In summary, in neonates with TGA after the arterial switch operation, positive pressure ventilation augments left ventricular filling during early inspiration, as evidenced by the changes in the Doppler flow velocities. When the inspiratory time is long in comparison to the intrinsic heart rate, there is a reduction in left ventricular filling during late inspiration and early expiration, also evidenced by the changes in the Doppler flow velocities. There were no changes in the Doppler measures of left ventricular relaxation and compliance.

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