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اصول تنظیم قراردادها

آموزش مهارت های کاربردی در تدوین و چاپ مقاله
Assessment of Left Atrial Ejection Force in Mildly Asphyxiated Newborns

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Abstract

Objective: Asphyxia-induced cardiac insult is one of the major causes of mortality and morbidity in the course of perinatal asphyxia. Nowadays, a remarkable trend of interest is sensed introducing a plausible modality for early detection of cardiac insults at the beginning stages of asphyxia. In this study we aimed to evaluate diagnostic utility of transmitral Doppler-derived parameters as well as left atrial ejection force index as a marker of left atrial contractile function in these patients.

Methods: In a prospective study selected cases of 26 asphyxiated newborns with preserved systolic function underwent conventional transmitral Doppler flow echocardiographic assessment. Left atrial ejection force index was further calculated for all patients. Data was compared with normal ranges of healthy newborns in order to clarify the diagnostic utility of these parameters for determining minor cardiac insults in this age group.

Findings: We found that mildly asphyxiated newborns showed an increase in the values of left atrial ejection force index (5.44±2.12 kilodyne vs. 6.66±2.17 kilodyne, P= 0.02) and left atrial filling fraction (39%±10% vs. 45%±8%, P= 0.01). Furthermore, the acceleration and deceleration rate of early filling flow peak velocity were decreased in this group of asphyxiated newborns.

Conclusion: Assessment of left atrial ejection force in mildly asphyxiated newborns reveals that newborns with even mild asphyxia, although could not be categorized in conventional grading system, suffer to some extent from a ventricular filling abnormality. This type of latent ventricular filling abnormality could simply be unmasked by calculation of atrial ejection force index.

Key Words: Neonate; Newborn; Asphyxia; Echocardiography; Atrial Function; Atrial Ejection Force

Introduction

Atrial ejection force (AEF) is a transmitral Doppler-derived parameter which reflects atrial contractile function¹⁴. It is defined as the force exerted by the atrium to push the blood through atrioventricular valve during atrial systole. Changes in atrial contractile function are subject to the pattern of left ventricular filling. In fact, AEF represents the proportion of contribution of atrium in diastolic performance of the heart²⁵. It has now been shown that changes in AEF correspond to early diastolic dysfunction of the ventricles which could not definitely be displayed by conventional diastolic assessment of the heart⁶⁷.
Today it is well understood that asphyxia has impact on the performance of the heart through ischemic injury\textsuperscript{[8-11]} and many parameters have been introduced to diagnose and estimate severity of this cardiac insult. However, the vulnerability of heart in the very beginning stages of asphyxia has not been investigated.

Here, our aim was to compare transmitral Doppler-derived parameters in normal and mildly asphyxiated newborns to investigate potential diagnostic utility of Doppler-derived AEF as a noninvasive assessment of ventricular filling capacity.

**Subjects and Methods**

We designed a prospective observational study which was carried out in the neonatal intensive care unit (NICU) of our institution. From February 2008 to March 2009 any mild asphyxiated newborn infant with preserved systolic function was enrolled into the study. To define asphyxia has occurred we considered umbilical artery base deficit >12 mmol/L. Mild asphyxia was defined as a 5 minute Apgar score ranging between 7 and 9 with an arterial pH between 7.2 and 7.3\textsuperscript{[12]}. Findings of minor abnormal encephalopathy or minor cardiovascular, respiratory or renal complications may also be presented in mild asphyxia (if any). Newborn encephalopathy was classified as minor if it consisted of jitteriness and irritability\textsuperscript{[13]}. Furthermore, classification as minor for organ complications was based on the following definitions\textsuperscript{[13]}; for cardiovascular system if there was just bradycardia or tachycardia (defined by the 95% confidence limits for heart rate for term and preterm newborns). For respiratory and renal systems respectively, if there was a need for just supplementary oxygen and observation of hematuria, but no increase in serum creatinine level.

The control group consisted of full term neonates who had 5 min Apgar scores >9 and pH >7.3 and had no signs of cardiovascular, respiratory and renal complications as previously described\textsuperscript{[5]}. The study protocol was approved by our institute committee of ethics and informed consent was obtained from parents of the newborns. The exclusion criteria of the study were the presence of left ventricular systolic dysfunction (left ventricular fractional shortening of less than 28%), requirement of mechanical ventilation, signs of heart failure, presence of congenital abnormalities or valvular diseases or congenital infections, inborn errors of metabolism and respiratory depression due to maternal sedation.

All selected asphyxiated newborns had underwent echocardiographic evaluation with VingMed 750 echocardiography machine (Sonotron, Horten, Norway), using a 5 MHz Doppler transducer. Sedative agents were not used during the echocardiographic examination. Left ventricular fractional shortening (FS) was calculated by M-mode and those with FS of less than 28% were considered to have a systolic ventricular dysfunction and were excluded from the study.

The transmitral pulsed Doppler velocity recordings from 5 consecutive cardiac cycles were used to derive transmitral Doppler-derived parameters including early filling peak wave velocity (peak E cm/s), atrial filling peak wave velocity (peak A cm/s), E/A ratio, E and A acceleration and deceleration rates (cm/s\textsuperscript{2}), rapid filling fraction and atrial filling fraction. The left atrial ejection force (LAEF), as previously described by Manning, et al\textsuperscript{[14]} was calculated by the following formula:

$$AEF = 0.5 \times \rho \times MVA \times (\text{peak A velocity})^2$$

In the formula, MVA stands for the mitral valve area and $\rho$ is the density of the blood. Mitral valve area was calculated as $d^2/4$, where $d$ is the mitral valve diameter estimated from the apical four chambers view. The LAEF was further divided by the value of body surface area to calculate the LAEF index.

Statistical package for social sciences (SPSS) version 15 was used for arranging descriptive statistics and for comparing study values with normal values previously published by our team\textsuperscript{[5]}. Independent samples t-test was used for comparing the normally distributed variables between two groups.
### Table 1: Baseline characteristics in normal and asphyxiated newborns

<table>
<thead>
<tr>
<th>Variables</th>
<th>Asphyxiated newborns (n=26)</th>
<th>Normal newborns (n=47)*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (days)</td>
<td>8.19 (6.41)</td>
<td>9.3 (3.1)</td>
<td>0.32</td>
</tr>
<tr>
<td>body surface area (m²)</td>
<td>0.20 (0.03)</td>
<td>0.21 (0.02)</td>
<td>0.09</td>
</tr>
<tr>
<td>Weight (gram)</td>
<td>2941 (765)</td>
<td>3113 (524)</td>
<td>0.26</td>
</tr>
<tr>
<td>Mitral valve area (cm²)</td>
<td>0.86 (0.15)</td>
<td>0.94 (0.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Heart rates (beat/minute)</td>
<td>121 (13)</td>
<td>127 (12)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

* Data retrieved from previous study of authors [5]

### Findings

The study population consisted of 26 asphyxiated newborn infants of whom 15 were male and 11 were female. The mean±standard deviations of the age were 8.2±6.4 (days) and for the weight and body surface area 2941±765 (g) and 0.20±0.03 (m²) respectively. As shown in Table 1, data was matched with that of the previous study [5]. However, the mean±standard deviation of the LAEF in asphyxiated newborns with preserved systolic function was more than in healthy newborns (Table 2). The value of P (statistical significance) decreased when LAEF indexed by BSA.

Comparison of transmitral Doppler-derived values between asphyxiated and healthy newborns is depicted in Table 2.

As shown in Table 2 atrial filling fraction increased in asphyxiated newborns and both E wave acceleration and deceleration times were decreased.

### Discussion

In this study, selective cases of asphyxiated newborns underwent echocardiographic transmitral Doppler flow evaluation and AEF values were calculated for all the patients. The selected cases were those in which there was no systolic ventricular dysfunction and none of them had signs of heart failure. In order to classify our group of interest we used a group of asphyxiated newborns previously described by Barberi et al [12], in which mild asphyxia was defined as a 5 minute Apgar score ranging between 7 and 9, and arterial blood pH between 7.2 and 7.3.

In a recently published study we suggested that complex aspects of diastolic dysfunction in newborns could be assessed more precisely by determination of AEF in this age group [5]. Similarly, comparing the mean values of the transmitral Doppler derived parameters shows that mild asphyxiated newborns could not be categorized in

### Table 2: Comparison of transmitral Doppler-derived echocardiographic values between normal and asphyxiated newborns

<table>
<thead>
<tr>
<th>Variables*</th>
<th>Normal newborns</th>
<th>Asphyxiated newborns</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid filling phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E peak velocity (cm/s)</td>
<td>58.6±9.2</td>
<td>54.5±10.86</td>
<td>0.09</td>
</tr>
<tr>
<td>E acceleration rate (cm/s²)</td>
<td>1194±244</td>
<td>949±195</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E deceleration rate (cm/s²)</td>
<td>648±119</td>
<td>487±119</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rapid filling fraction (%)</td>
<td>57±9</td>
<td>53±8</td>
<td>0.06</td>
</tr>
<tr>
<td>Atrial filling phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A peak velocity (cm/s)</td>
<td>49.2±8.8</td>
<td>51.1±7.2</td>
<td>0.3</td>
</tr>
<tr>
<td>A acceleration rate (cm/s²)</td>
<td>873±150</td>
<td>869±185</td>
<td>0.9</td>
</tr>
<tr>
<td>A deceleration rate (cm/s²)</td>
<td>981±277</td>
<td>889±232</td>
<td>0.1</td>
</tr>
<tr>
<td>Atrial filling fraction (%)</td>
<td>39±10</td>
<td>45±8</td>
<td>0.01</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.22±0.25</td>
<td>1.11±0.23</td>
<td>0.07</td>
</tr>
<tr>
<td>AEF (kilodyne)</td>
<td>1.12±0.42</td>
<td>1.35±0.5</td>
<td>0.04</td>
</tr>
<tr>
<td>AEF Index (kilodyne/m²)</td>
<td>5.44±2.12</td>
<td>6.66±2.17</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* All data collected for the left ventricle

E: Early filling flow peak velocity; A: Atrial filling flow peak velocity; AEF: Atrial ejection force
any of the three stages of diastolic dysfunction (impaired relaxation, pseudonormalization and restrictive pattern as described by O’Leary and his colleagues[15,16]). As shown in Table 2 the mean E/A ratio is not significantly different between the two groups. Hence, using common definition of diastolic dysfunction for these asphyxiated newborns falsely would lead to consider them as having a normal diastolic function. However, comparison of LAEF index between the two groups reveals the presence of at least a minimum ventricular abnormality in mildly asphyxiated newborns. Previously it was described that rise in LAEF in otherwise normal ventricular function (those patients which could not be categorized in any of the three diastolic dysfunction grades, as described above) could represent a subclinical (latent) diastolic dysfunction[5-7]. These results raise the question that asphyxiated newborn infants, even without any apparent systolic dysfunction, suffer from a latent diastolic dysfunction, which could be disclosed by the assessment of atrial contractile function in this group of patients. Increased left atrial filling fraction in asphyxiated newborns, in conjunction with increased LAEF index, as a simple and reproducible way of assessing atrial contractile function, supports the presence of diastolic filling abnormality in this age group (Table 2).

LAEF, an estimate of the contractile function of the left atrium, together with indexes of atrial size, have prognostic implications upon adverse cardiovascular events and their outcomes[17,18]. However, what we sought in this study was the diagnostic utility of LAEF to reveal the presence of minor modification in diastolic function of left ventricle.

Diagnostic application of LAEF has been assessed in different surveys. For example it has been introduced as a sensitive parameter to detect left ventricular diastolic abnormalities in autoimmune diseases[6] or left ventricular systolic deterioration in patients with hypertension[19].

Asphyxiated newborns have heart rates of greater than normal values[11]. It also has been shown that increased heart rate could raise the value of AEF[5]. Comparison of heart rates between normal subjects and asphyxiated ones represents no significant change between groups (Table 1). Therefore, heart rate could not play a confounder role in our explanation.

It is worthy to declare that based on our findings, the transmitral flow diagram in the newborns with asphyxia was slightly different in shape with that of normal newborns. Up slope in E acceleration rate and down slope in E deceleration rate diagrams were decreased in asphyxiated newborns in favor of abnormal ventricular relaxation. These findings represent that even in early stages of diastolic filling abnormality the time needed for ventricular filling, even without the force exerted by atrium, is prolonged. A phenomenon seems to exist to compensate the process of ventricular stiffness at its beginning.

Although the value of $P$ for the latter variables are enough small to introduce them as a suitable predictors of diastolic dysfunction, there is not any strong pathophysiological rational to justify the occurrence of such changes exactly as a result of or just before ventricular stiffness. Surely, further studies with larger sample sizes are necessary to clarify the exact relation between these suggested parameters and diastolic dysfunction in newborns.

**Limitations:** Atrial contractile function consists of several volumes, indexes and volume fractions, as described by investigators[4,7,20]. In this study, we just made use of some of the simplest and more reproducible variables: AEF index and transmitral Doppler-derived indexes as well as atrial filling fraction. Undoubtedly, a comprehensive study would reveal the presumed diastolic abnormality more precisely.

**Conclusion**

Augmentation of the left atrial contractile function as well as LAEF and atrial filling fraction in asphyxiated newborns beyond the normal values obtained in our study could be a reflection of undetectable left ventricular relaxation abnormalities (latent diastolic dysfunction) and may predict their development in the course of myocardial disease.

Regarding the clinical significance of disclosure of cardiac insult in the very beginning stages of
Asphyxia, our finding justifies securing attention for the precise cardiac follow-up of neonates with history of even mild asphyxia. Moreover, this finding again highlights the unique diagnostic capability of atrial ejection force to unmask the presence of latent diastolic filling dysfunction.

**Acknowledgment**

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**Conflict of Interest:** None

**References**

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