Determination of cardiac reserve in preterm infants

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We aimed in this study to determine the cardiac reserve in preterm infants with phonocardiogram. One hundred and fifty-four preterm infants participated in this study. The ratio of the first heart sound to the second heart sound (S1/S2), the ratio of diastolic to systolic duration (D/S) and the cardiac contractility change trend after stimulation (CCCTS) were measured in all infants. The preterm neonatal S1/S2 decreased with increasing gestational age, but the differences between each gestational stage were not significant ($p>0.05$), while the D/S significantly increased with increasing gestational age ($p<0.05$). After crying induced by vaccination, the D/S was significantly lower than that in quiet state at each gestational stage ($p<0.05$). The CCCTS increased with increasing gestational weeks, but the differences between each gestational stage were not significant ($p>0.05$)

Key words: cardiac reserve, phonocardiogram test, preterm infant, S1:S2 ratio, D:S ratio, cardiac contractility change trend after stimulation.

As the result of incomplete development of the cardiovascular system, the neonate, especially the preterm infant, seems particularly susceptible to heart diseases, even heart failure, in the absence of structural heart disfigurement. Although the early cardiac trauma induced by heart diseases could just be temporary myocardial hypoxia-ischemia and be repaired easily, as it presents with atypical symptoms, neonatal heart failure can rarely be diagnosed in the early stage, and thus can rapidly threaten the neonatal life. It is therefore important to detect neonatal heart failure in the early stage.

It has been proven that in most cases of heart failure, the primary and initial pathologic event is a reduction in cardiac reserve (CR), which is the ability to augment cardiac function to meet demands and consists of heart rate reserve[1], diastole volume reserve[2], systole volume reserve[3], coronary reserve[4], metabolic reserve[5], and plasma norepinephrine reserve[6], etc., and especially the reduction of myocardial contractility[7-10]. Researches about the very close relationship between amplitude of the first heart sound (S1) and myocardial contractility[11,12] offered a new way to evaluate cardiac function. Systematic studies were conducted in various populations by using phonocardiogram exercise testing (PCGET), and the results showed the S1 amplitude change trend could provide a noninvasive assessment of CR.

However, there are many factors that can influence the absolute amplitude of heart sound, such as gender, age, different postures, respiratory depth, the thickness of the chest wall, and the position of the sensor on the chest wall, etc., which indicate that the absolute amplitude of S1 cannot be used as an indicator for evaluating cardiac contractility. It is reported that the cardiac contractility change trend (CCCT), defined as the increase in the S1 amplitude after accomplishing different exercise workloads with respect to the amplitude of the S1 recorded at rest; the ratio of the amplitude of S1 to the amplitude of the second heart sound (S2) (S1/S2); and the ratio of diastolic to systolic duration (D/S) tested by the phonocardiogram testing (PCGT) could avoid these influences[13-15], reflect the cardiac contractility, and evaluate whether the time in diastole, which decides how much nutrition and oxygen the myocardium could gain, is sufficient[13].

Table I. The Characteristics of Preterm Infants

Gestational age	Number	Birth weight	Birth length	1 min Apgar Score ≤7 (%)
28-31$^{6/7}$	14	1349.55±339.19	40.59±3.85	10 (71.43)
32-33$^{6/7}$	23	1822.50±355.47	42.55±2.50	5 (21.74)
34-36$^{6/7}$	117	2479.18±450.73	45.98±2.32	12 (10.26)
P		<0.05†	<0.05†	<0.05†

† The differences of preterm neonatal birth weight, birth length and percent of 1 min Apgar score ≤7 between each gestational stage were significant ($p<0.05$).

The primary objective of this work was to determine the CR in preterm infants using the PCGT for the first time. Because the neonates cannot undertake an exercise test, we brought forward the CCCT after stimulation (CCCTS), which was defined as the increase of the S1 amplitude after crying induced by the same stimulation (vaccination) with respect to the amplitude of the S1 recorded at rest, to replace the CCCT.

Material and Methods

We recorded phonocardiograms of 154 preterm infants who were born from 1 November 2007 to 30 August 2011 in the Department of Obstetrics, West China Second University Hospital. The study was approved by the Ethical Commission of the West China Second University Hospital. Written parental informed consent was obtained for all subjects.

The preterm infant was included if it met the following criterias: 1. Gestational age was between 28 and 36$^{6/7}$ weeks (according to the Chinese definition of preterm infants), and 2. Singleton pregnancy.

The Exercise Cardiac Contractility Monitor (ECCM, developed by Bo-Jing Medical Informatics Institute, Chongqing, China) was used for this investigation. The hardware of ECCM consists of a phonocardiographic (PCG) sensor, a heart sound signal preprocessing box, a computer, and a printer. ECCM uses a sampling rate of 8 KHz with 8 bits per sample (monochannel). The software includes a fundamental heart sound measurement system.

The phonocardiograms were recorded from the neonatal apex by placing the PCG sensor on the chest surface. The examination was started after newborn resuscitation, when the baby had breathed quietly in supine position, and immediately after crying, which was induced by the vaccination. In order to avoid human-induced errors, only one testing operator was required to press the sensor with similar strength against the cardiac apex area of each volunteer's chest. The operator controlled the test time strictly to ensure all the phonocardiograms were recorded at the same time between babies. Each phonogram was recorded twice and at least five cardiac cycles were recorded.

The Kolmogorov-Smirnov test was used to verify whether the data were distributed normally. Numerical values are presented as mean±standard deviation (SD). The median was provided to describe the distribution of non-normally distributed data. The Mann-Whitney U, Kruskal-Wallis test and one-way ANOVA were used to compare groups where appropriate. The chi-square test was used for categorical variables. P-values of less than 0.05 were deemed to be significant. Numerical values are presented as mean±SD.

Results

In China, preterm births are classified into three stages: very preterm (28-31$^{6/7}$weeks), moderate preterm (32-33$^{6/7}$weeks) and mild preterm (34-36$^{6/7}$ weeks). According to this classification, there were 154 preterm infants volunteering to participate in this study. Their characteristics are shown in Table I. The results showed that the differences in preterm neonatal birth weight, birth length and percent of 1 min Apgar score ≤7 between each gestational stage were significant ($p<0.05$).

The results of the Kolmogorov-Smirnov test for normality of distribution showed that the distribution of preterm neonatal S1/S2 was not normal while that of D/S was normal. The data of S1/S2 and D/S were reported as the median and mean±SD, as shown in Table II. The results showed that the preterm neonatal

Table II. The Data of S1/S2 and D/S of Preterm Infants at Different Gestational Weeks

Gestational age	Number	S1/S2	D/S
28-31$^{6/7}$	14	1.52	0.80±0.13
32-33$^{6/7}$	23	0.94	0.89±0.23
34-36$^{6/7}$	117	0.88	0.93±0.15
P		>0.05†	<0.05‡

S1/S2: Ratio of the amplitude of the first heart sound to the amplitude of the second heart sound. D/S: Ratio of diastolic to systolic duration.
† Of S1/S2, the differences between each gestational stage were not significant (p>0.05).
‡ Of D/S, the differences between each gestational stage were significant (p<0.05).

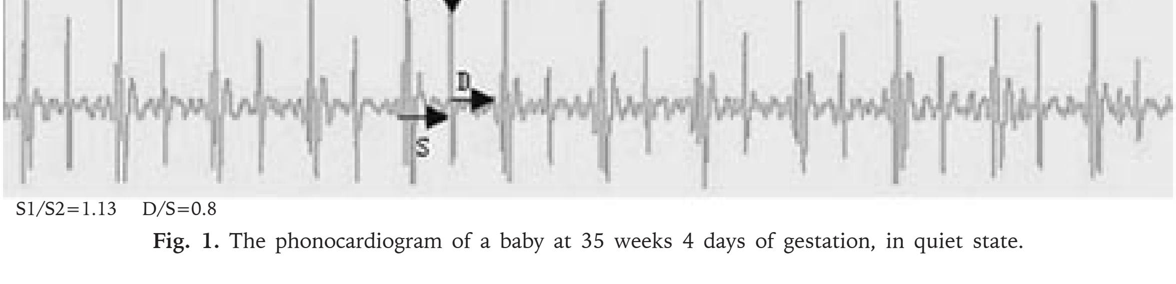
average S1/S2 decreased with an increase in the gestational age, but the differences between each gestational stage were not significant (p>0.05), while the D/S significantly increased with an increase in the gestational age (p<0.05).

We also recorded phonocardiograms of 87 preterm infants after crying induced by vaccination. Their S1/S2 and D/S data in quiet state and after crying at different gestational weeks were reported as the median and mean±SD, as shown in Table III. The results showed that after crying, the preterm neonatal S1/S2 increased, but only the difference at 34-36$^{6/7}$ weeks was significant (p<0.05). After crying, the preterm neonatal D/S was significantly lower than that in quiet state at each gestational stage (p<0.05). The phonocardiograms of a baby at 35 weeks 4 days of gestation that were recorded in quiet state and after crying are shown in Figures 1 and 2.

The results of the Kolmogorov-Smirnov test for normality of distribution showed that the distribution of preterm neonatal CCCTS was not normal. The data of CCCTS were reported as the median, as shown in Table IV. According to the results, the preterm neonatal CCCTS increased with an increase in gestational weeks, but the differences between each gestational stage were not significant (p>0.05).

Discussion

An ideal method for cardiac function evaluation should be noninvasive, with high benefit/cost ratio, and portable for use. Nowadays, there are many methods for measuring and evaluating cardiac function, but all of them have disadvantages. For example, electrocardiogram examination is the optimal method for monitoring myocardial chronotropism and dromotropism; however, it is unable to monitor inotropism. Chest X-ray is useful when heart disease is suspected clinically; however, slight heart enlargement cannot be detected accurately by radiography. Cardiac catheterization is objective and quantitative, but it is an invasive procedure, requires a special catheterization area, aseptic manipulation, and cannot be used routinely. Cardiac blood-pool developing with radionuclide and nuclear magnetic resonance detection has high sensitivity and specificity, but is expensive and not easy to popularize. Maximal oxygen uptake (VO_2 max) and anaerobic metabolism threshold determination are objective, practical and



S1/S2=1.13 D/S=0.8

Fig. 1. The phonocardiogram of a baby at 35 weeks 4 days of gestation, in quiet state.

S1/S2=2.15 D/S=0.7 CCCT S=1.65

Fig. 2. The phonocardiogram of a baby at 35 weeks 4 days of gestation, after crying.

quantitative, but are affected by respiratory function. Furthermore, it can only be used in a special laboratory, requiring complex equipment and professional technicians. Thus, they are not appropriate for daily use. Echocardiography can be used to measure and evaluate cardiac function noninvasively, structurally and functionally, and has become the chief method to examine an infant's cardiovascular system. However, it requires a long time to complete the whole examination and it is not cheap. Researchers have used the tilt-table test to evaluate the myocardial performance and baroreceptor reflexes in preterm neonates[16]. The disadvantage of this method is that it cannot monitor inotropism and cannot be used in preterm infants with severe complications.

It was found that the changes in the amplitude of S1 are closely related with the maximum rate of increase in left ventricular pressure ($r=0.9551$, $p<0.001$), and the change trend of the amplitude of S1 can be used to evaluate CR and cardiac endurance. Based on these discoveries, Xiao et al.[17] introduced the PCGET to test the CCCT. Then, studies were conducted to test the usefulness of the CCCT[18] and to compare the CCCT with the methods and indicators that had been widely used to evaluate cardiac function, such as ejection fraction (EF), VO_2 max, maximum elasticity (Emax), the New York Heart Association's functional classification (NYHA FC), and the 6-minute walk test[19]. The results showed that the sensitivity, specificity and accuracy of CCCT for evaluating cardiac inotropism state were 96%, 100% and 100%, respectively. Cardiac function as tested by CCCT was closely related with that by EF, VO_2 max and Emax ($r=0.728$, 0.90, and 0.702, respectively, $p<0.01$) and the results had a good relationship with the NYHA FC and 6-minute walk test. In addition, the CCCT test takes about 10 seconds, and the cost for one case was¥30, which is much cheaper than when using any other method. Thus, it was concluded that the PCGET can offer the

Table III. The Average Data of S1/S2, D/S of Preterm Infants in Quiet State and After Crying at Different Gestational Weeks

Gestational weeks	Number	S1/S2		D/S	
		Quiet	Crying	Quiet	Crying
$28\text{-}31^{6/7}$	7	1.04	1.08	0.72±0.09	0.64±0.10
$32\text{-}33^{6/7}$	12	0.96	1.00	0.79±0.17	0.68±0.14
$34\text{-}36^{6/7}$	68	0.75		0.85±0.17	
		0.99		0.82±0.17	
P		<0.05†		<0.05‡	

S1/S2: Ratio of the amplitude of the first heart sound to the amplitude of the second heart sound. D/S: Ratio of diastolic to systolic duration.

† After crying, only the difference of S1/S2 at $34\text{-}36^{6/7}$ weeks was significant ($p<0.05$).

‡ After crying, the preterm neonatal D/S was significantly lower than that in the quiet state at each gestational stage ($p<0.05$).

Table IV. The CCCTS of Preterm Infants at Different Gestational Weeks

Gestational weeks	Number	CCCTS
28-31$^{6/7}$weeks	7	1.37
32-33$^{6/7}$weeks	12	1.41
34-36$^{6/7}$weeks	68	1.47
P		>0.05†

CCCTS: Cardiac contractility change trend after stimulation.
† There were no significant differences between each stage (p>0.05).

advantages of being noninvasive, convenient, objective, quantitative, repeatable, and with high benefit/cost ratio for measuring and evaluating cardiac contractility and CR.

It is reported that in addition to eliminating the influences that come from gender, age, different postures, respiratory depth, thickness of the chest wall, and position of the sensor on the chest wall, etc. on the absolute amplitude of heart sound, the S1/S2 ratio could reflect the relationship between the cardiac contractility and the peripheral resistance[14] and significantly discriminate normal from reduced left ventricular pressure rise (LV dP/dt) and EF[15]. Moreover, whether or not the time in diastole, when myocardial blood perfusion occurs, is sufficient relates to how much nutrition and oxygen will be available during systole. This availability depends on the state of myocardial metabolism, and relates to ventricular filling and cardiac output. The longer the time in diastole, the more nutrition and oxygen the myocardium could gain, and the stronger the CR. Thus, D/S is a indicator that can be used to determine the CR[13].

Our study showed that preterm neonatal S1/S2 decreased with an increase in gestational age, but the differences between each gestational stage were not significant, while the D/S significantly increased with an increase in gestational age. This indicated that with increasing gestational age, the preterm neonatal cardiac contractility reserve improved, including a decrease in the myocardial contractility and prolongation in the myocardial perfusion time, in accordance with the human organic growth rule.

The CR tested in quiet state and after crying reflected that the stimulation would result in preterm neonatal myocardial contractility augmentation and reduction in myocardial perfusion time in diastole. Namely, the crying after stimulation would reduce the CR of preterm infants. Preterm infants at earlier gestational ages, when faced with the same stimulation, are more susceptible to the heart diseases since they have lower CR.

The results of CCCTS in our study showed that the CCCTS increased with an increase in gestational age, although there were no significant differences between each stage (p>0.05). It reflected that with an increase in gestational age, the preterm neonatal CCCT improved, namely, the CR improved. This was also in accordance with the human organic growth rule.

From the results of this study, we obtained primary data of CR in preterm infants. The data demonstrated that the longer the gestational age, the stronger the CR of a preterm infant. We should strengthen the care of cardiac function in preterm neonates at earlier gestational ages.

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