中山醫學院醫學研究所碩士論文

Master Thesis, Institute of Medicine,

Chung Shan Medical and Dental College

指導教授：陳家玉　教授

以超音波評估早產兒與足月兒膽囊容積及收縮的正常值和臨床上的應用

Gallbladder volume and contractility in term and preterm neonates: normal values and clinical applications in ultrasonography

研究生：何茂霖 （Mao-Lin Ho）撰

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中華民國八十八年六月九日

授權書
(博碩士論文)

本授權書所授權之論文爲本人在 中山醫 大學(學院) 醫學研究 系所

臨床醫學 組 八十七 學年度第 二 學期取得 碩 士學位之論文。

論文名稱： **Gallbladder volume and contractility in term and preterm neonates: normal values and clinical applications**

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日期：民國 88 年 6 月 17 日

1. 本授權書請以黑筆撰寫並影印裝訂於書名頁之次頁。

本論文爲中山醫學院授與醫學碩士學位之必備條件之一，經中山醫學院醫學研究所碩士論文考試委員會審查合格及口試通過。

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(論文指導教授)

中　華　民　國　八　十　八　年　六　月

學生何茂霖論文題目為 Gallbladder volume and contractility in term and preterm neonates: normal values and clinical applications in ultrasonography，其論文已經中山醫學院醫學研究所碩士論文考試委員會審查合格及口試通過，並由其指導教授核閱後無誤。

指導教授：

私立中山醫學院醫學研究所教授　　陳家玉 博士

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中　華　民　國　八　十　八　年　六　月　一　日

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摘　要

本研究的目的乃是利用超音波來測量早產兒及足月兒的膽囊容積和收縮並評估相關因子；吾人是以橢圓形方法用超音波來測量50位早產兒及46位足月兒的膽囊容積，且測量的時間是在剛出生、出生後6小時、以及接受規則餵奶後經過3小時和6小時的禁食，每隔十五分鐘持續一小時並計算其膽囊容積和收縮指數；膽囊收縮指數是由餵奶後容積的減少量除以禁食後的起始容積。膽囊容積和最大收縮率均以足月兒較爲大（$p < 0.05$），足月兒亦顯示出較易達到膽囊容積的最大收縮（$p < 0.05$）；早產兒膽囊容積的最大收縮需要在懷孕週數大於 31週或是體重大於 1300公克才較清楚觀察到。因此希望藉由瞭解禁食與餐後系列的膽囊容積和收縮之變化，可以提供吾人評估早產兒及足月兒是否有肝膽系統疾病的線索。關鍵字：收縮，收縮指數，橢圓形方法，禁食，膽囊容積，餐後，超音波。

Abstract

The aim of this study was to establish the normal values and evaluate associated factors of gallbladder volume and contractility in term and preterm neonates by using ultrasonography. Sonographic measurement of gallbladder volume was performed by using the ellipsoid method in 50 preterm and 46 term infants. We collected data soon and 6-hour fasting after delivery, at 3-hour and 6-hour fasting following regular milk feeding. Serial postprandial changes of gallbladder volume and contractility were collected at 15-minute intervals for one hour. Gallbladder contraction index (C.I.) was determined as percentage decrement of postprandial size from initial size. Both mean gallbladder volume and maximal contraction ratio were larger in term group ($P < 0.05$). Term neonates demonstrated significant contraction more readily (C.I. > 50%) ($P < 0.05$). In preterm infants, significant contraction was clearly observed only at postconceptional age above 31 weeks or when their body weight above 1300 gm. A better understanding of gallbladder physiology and its fasting or postprandial sonographic morphology would facilitate sonographic evaluation for the presence of hepatobiliary diseases in preterm and term neonates. □Contractility, contraction index, ellipsoid method, fasting, gallbladder volume, postprandially, ultrasonography.

The development of gallbladder function depends on integrated maturation of its digestive, absorptive, and motor functions. Adequate bile acid excretion into the intestines enhances fat absorption. Cholecystokinin (CCK) plays an important role in regulating basal gallbladder tone and postprandial gallbladder contraction.[1-3] The secretion of CCK is chiefly stimulated by fat, protein, and amino acid, and to a lesser degree by glucose.[4-6]

Ultrasonography is a well-established and non-invasive technique to evaluate gallbladder.[7] Several imaging methods are available to measure and evaluate gallbladder volume and contractility after a fatty meal in the past. These include serial contraction index, significant contraction index (C.I. > 50%), time to peak contraction and time to refilling.[7-9] However, little is known about the size and the degree of gallbladder contraction in term and preterm neonates.[9,10] It is the aim of this study to evaluate gallbladder volume and contractility in term and preterm neonates.

By assessing the serial changes of postprandial gallbladder volumes, we can realize the physiology of gallbladder function and reach a better understanding of gallbladder volume and contractility in term neonates as well as premature infants. It is also the aim of this study to establish the normal values and evaluate associated factors regulating gallbladder volume and contractility, which might give clues to the presence of hepatobiliary diseases.

Patients and methods

This study was performed in normal nursery room and neonatal intensive care unit of Chung Shan Medical College Hospital, a teaching medical college hospital, from

July 1995 to February 1997. There were 46 term and 50 preterm (gestation age 27 - 35 weeks) babies included in this study. All cases with hemodynamic instabilities, sepsis, use of opioids and any evidence of abdominal pathology were excluded (table 1). Ultrasound examination was performed by using the Aloka Echocamera SSD-630 (Aloka Ltd, Mitaka-Shi, Tokyo, Japan) equipped with 5.0 MHz transducer. Applying the ellipsoid method, sagittal and transverse scans of gallbladder at its maximum dimensions were acquired. Each parameter was measured three times consecutively and the mean maximum length, width, and height were calculated. Gallbladder volume was calculated from the equation[7]: lengthx widthx heightx π/6. The method error as the percentage of the mean volume was 9.8%.

We collected gallbladder volume soon and 6-hour fasting after delivery, at 3-hour and 6-hour fasting following regular milk feeding. Serial postprandial changes of gallbladder volume and contractility were collected at 15-minute intervals for one hour. The test meal consisted of breast milk or infant formula and 10% glucose water, which amount was equivalent to that of the usual meal of the same age neonates. Postprandial gallbladder contractility was also compared in infants between feeding 10% glucose water at the third hour of fasting and only with parenteral nutrition during 6-hour fasting period.

From the above data we determined the contraction index (C.I.). The C.I. was defined as % decrement of gallbladder size from the initial size {C.I. (%) = (fasting size $-$postprandial size) / fasting sizex 100 (%)}. The evaluation of gallbladder contractility adopted significant contraction (C.I. >50%) at 30 and 45 minutes after feeding and maximal contraction ratio at 60 minutes postprandially. In preterm neonates we continued to measure gallbladder volume every week until their body

weight to 2400 gm and postconceptional age to 38 weeks.

Data were expressed as median and standard deviation range. Absolute gallbladder volumes, rather than percentage change, were compared. Comparisons between groups were made using the Student-t test. Differences were regarded as significant if P value <0.05.

Results

Gallbladders were visualized in all term and preterm neonates in our study. The mean gallbladder volume was larger in term group ($P < 0.05$). There was no significant gallbladder contraction during the immediate six hours after delivery (table 2). Initiation of regular milk feeding resulted in contractional changes of gallbladder volume within 24 hours after delivery in term neonates (figure 1). The 3-hour fasting gallbladder volume became almost negligible in both term and preterm neonates (81.32 ± 59.43 mm^3 vs 88.29 ± 63.56 mm^3), indicating existence of good gallbladder contractility response to appropriate stimulus. The serial values of postprandial gallbladder volume in term neonates after 6-hour fasting were shown in figure 2. Gallbladder volumes of preterm infants were correlated with postconceptional age and postnatal body weight. Comparing gallbladder volume after 3-hour fasting with that after 6-hour fasting, the less deviation was noted in lower body weight infants, especially below 1300gm, or smaller postconceptional age infants, especially below 31 weeks (figure 3). This indicates that transient gallbladder dilatation or poor gallbladder contraction was present in early postnatal periods, especially in very low birth body weight infants.

The gallbladder contraction index (C.I.) was determined by the difference

between the size of postprandial 15, 30, 45 and 60 minutes and that of 6-hour fasting. In 10% glucose water feeding infants the gallbladder C.I. was 23.35% at 30 minutes and 27.65% at 60 minutes postprandially. In other words, there was only small and insignificant change in gallbladder volume with 10% glucose water feeding. There was also no significant difference in gallbladder contractility in infants between feeding 10% glucose water at the third hour of fasting and in infants with partial parenteral nutrition during 6-hour fasting period. In the design of this study, 10% glucose water served as substitute for one meal during 6-hour fasting period in order to obtain maximal gallbladder volume. This allowed 6 hours of milk abstention and prevented unnecessary fasting hypoglycemia.

Significant gallbladder contraction (C.I. > 50%) was achievable in more term neonates than preterm infants at 30-minute, 45-minute and 60-minute postprandial monitor: 70% vs 62%; 96% vs 88%; 100% vs 92%, respectively. 8% of preterm infants could not achieve the significant contraction at 60 minutes after feeding (figure 4). Accordingly, there is increasing ratio of achieving significant gallbladder contraction from 30 minutes postprandially in both term and preterm infants. The mean gallbladder contraction index and maximal contraction ratio were higher in term infants than in preterm infants (figure 5). This indicates there is stronger gallbladder contractility in term infants.

Gallbladder contractility was correlated with postconceptional age and body weight by using 30-minute significant contraction index. There was postconceptional age-dependent difference in gallbladder contractility in preterm neonates, which showed poor postprandial gallbladder contraction at postconceptional age below 31 weeks (figure 6). In addition, body weight showed positive correlation with gallbladder contractility: preterm infants with body weight above 1300 gm had the

potent ability to achieve 30-minute significant contraction index (figure 7).

Discussion

Gallbladder plays a unique role in the digestive, hormonal and peristaltic interplay between gastrointestinal tract and hepatobiliary system. The concentration and excretion of its bile acids and bilirubins, among other substances is mediated through several humoral factors, especially cholecystokinin (CCK), gastrin and motilin. CCK regulates basal tone and stimulates postprandial cholecystic contractile activity whereas bile acid enhances fats absorption and the absorbed fat stimulates duodenal CCK secretion. [1-3] The functional maturation of these inter-relationship is an additional important factor in neonates, especially preterm infants.

To evaluate gallbladder volume and contractility, it is necessary to observe its optimal size (after 6-hour fasting) and obvious contraction after appropriate stimulus. Breast milk or infant formula has adequate content of fat, proteins and amino acids to effect potent stimulus for CCK secretion. Other components, such as carbonate or vitamines, are less effective. [4-6] It is reasonable to substitute breast milk or infant formula for fatty meal as the stimulus in this study, since it involves neonates. For ethical reasons and to avoid fasting hypoglycemia, 10% glucose water was used at the third hour of fasting since it did not cause significant contraction: only 27.65% maximal contraction.

In this study, regular milk feeding resulted in very strong gallbladder contraction in term neonates within the first 24 hours after delivery. In absence of 6-hour fasting, gallbladder tended to maintain its slit-like (small size) morphology. The same might occur in preterm infants with postconceptional age above 31 weeks or

body weight above 1300 gm. The latter might be due to stress improvement (i.e. the influence of perinatal period and exposed environment), appropriate food stimulus and adequate hormone secretion.

Term neonates had larger fasting gallbladder volume than preterm infants ($p<0.05$). Correspondingly, they showed significant cholecystic contraction more readily and greater maximal contraction ratio than preterm infants. Gallbladder contraction is mainly mediated by CCK liberated from the duodenal mucosa as a consequence of the entry of foodstuff or gastric acid.[2, 3] The maturation sequence of postprandial CCK response is important in newborn infants, because CCK secretion initiated in the second trimester and increased only slightly during the third trimester. [11] Understandably, the postprandial CCK response is weaker in preterm infants. [12] In this study, preterm infants acquired demonstrable ability for significant 30-minute postprandial contraction at postconceptional age above 31 weeks or body weight above 1300 gm. There is an obvious sonographic window period in premature infants before adequate assessment of gallbladder function is imaginable. Postconceptional age and/or body weight are important determinants of gallbladder maturation and contractility. In other words, the optimal time for ultrasound evaluation of preterm infant should be selected at the postconceptional age above 31 weeks or body weight above 1300 gm.

In the presence of hepatobiliary diseases, gallbladder volume and contractility are adversely affected. Notably, Cholestasis due to prolonged parenteral nutrition is associated with abnormal hepatobiliary function.[13, 14] Gallbladder in these infants typically showed very small volume (slit-like) and occasionally gallstone or bile sludge.[15-17] Whether abnormal contractility would precede the onset of parenteral nutrition associated cholestasis and to what extent it would be affected

deserve further study.

Furthermore, small atretic gallbladder is usually associated with extrahepatic biliary atresia.[18, 19] Knowledge of normal data for 6-hour fasting gallbladder volume and postprandial contractility indices for preterm and term infants provides qualified data to the diagnosis of extrahepatic biliary atresia, especially in preterm infants. In addition, folding gallbladder can be differentiated from choledochal cyst based on postprandial contractility study.[20, 21]

In summary, 10% glucose water is used as a substitute for one meal to attain the "6-hour fasting" protocol in this study. Term neonates have larger gallbladder volume and show significant contraction than preterm infants more readily. In preterm infants, transient gallbladder dilatation or poor contraction during the early postnatal period may be categorized as "normal physiologic state", especially in very low birth body weight neonates. Significant gallbladder contraction is more likely in preterm infants after postconceptional age of 31 weeks or body weight above 1300 gm. A better understanding of gallbladder physiology and its fasting or postprandial sonographic morphology would facilitate sonographic evaluation for the presence of hepatobiliary diseases in preterm and term infants.

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Table 1. Characteristics of studied infants. Values as given as mean standard deviation (SD).

	Term neonates	Preterm neonates
No.	46	50
Gestational age (weeks)	38.30 ± 1.24	31.68 ± 2.49
Apgar score (1 min)	8.09 ± 0.81	5.14 ± 2.37
Apgar score (5 min)	9.83 ± 0.38	7.26 ± 1.77
BBW (g)	3253.26 ± 440.00	1556.00 ± 440.84

Exclude: haemadynamic instabilities, sepsis, use of opioids and any evidence of abdominal pathology.

BBW: birth body weight.

Table 2. Gallbladder volume of term and preterm infants.

Gallbladder volume (μl)	Term neonates	Preterm neonates
No. of observations	46	50
At birth	1123 (193 – 2357)	660 (143 – 1251)
6-h after birth	1013 (171 – 2188)	569 (139 – 1469)
After regular feeding		
No. of observations	46	294
6-h fasting	712 (117 – 1258 0	321 (118 – 896)
3-h fasting	79 (0 – 189)	82 (0 – 206)

Values given as median (ranges).

Mann-Whitney U test, $p < 0.05$.

Fig. 1. Changes of gallbladder volume. Term infants initiated to feed with 10% glucose water at the sixth and ninth hour after delivery; then milk was fed at the interval of 3 hours from the twelfth hour postnatally. Values as mean and standard deviation.

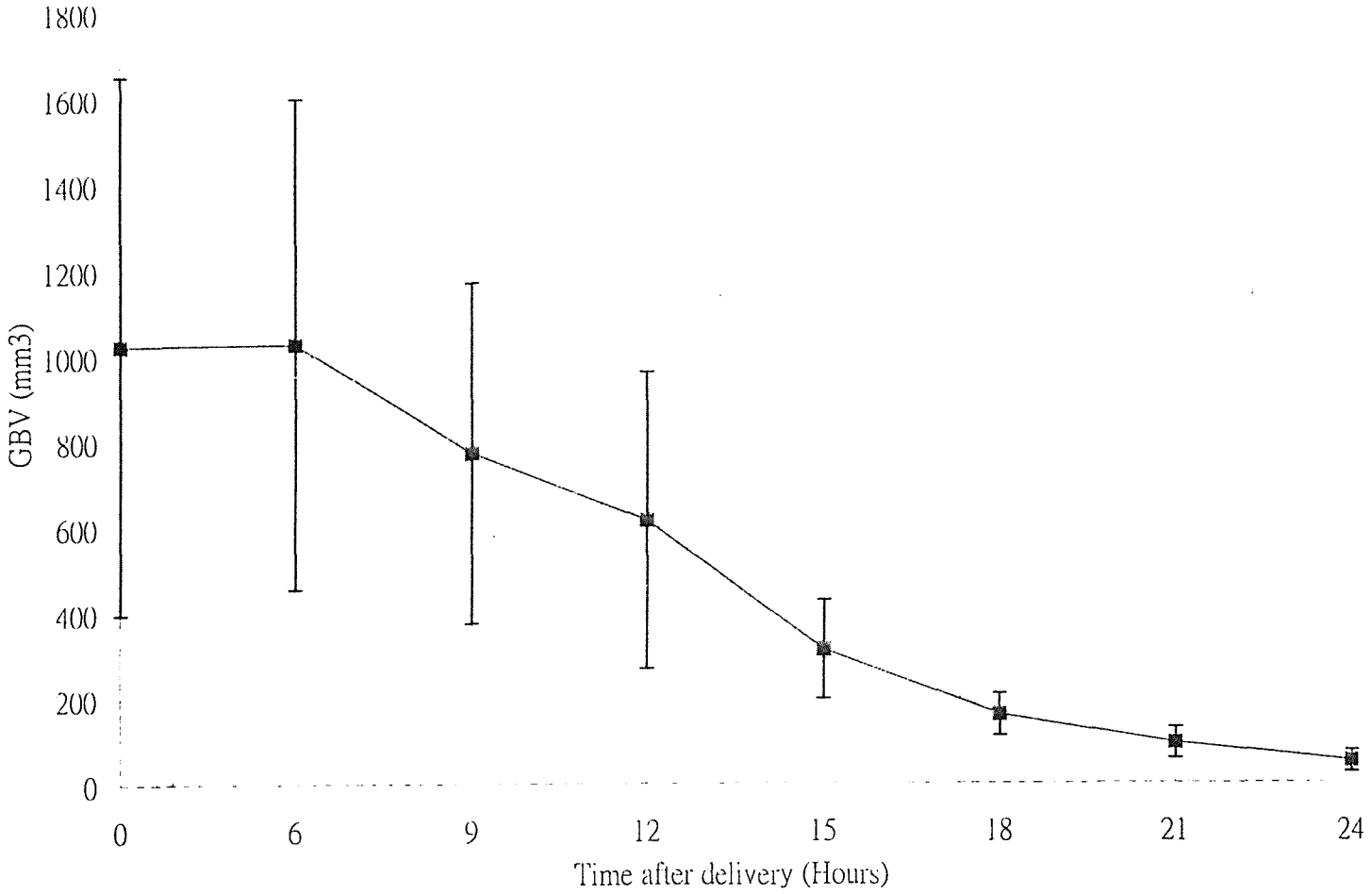

Fig. 2. The serial values of postprandial gallbladder volume in 3-5 days of age neonates at every 15-minute interval after 6-hour fasting period. Values as mean and standard deviation.

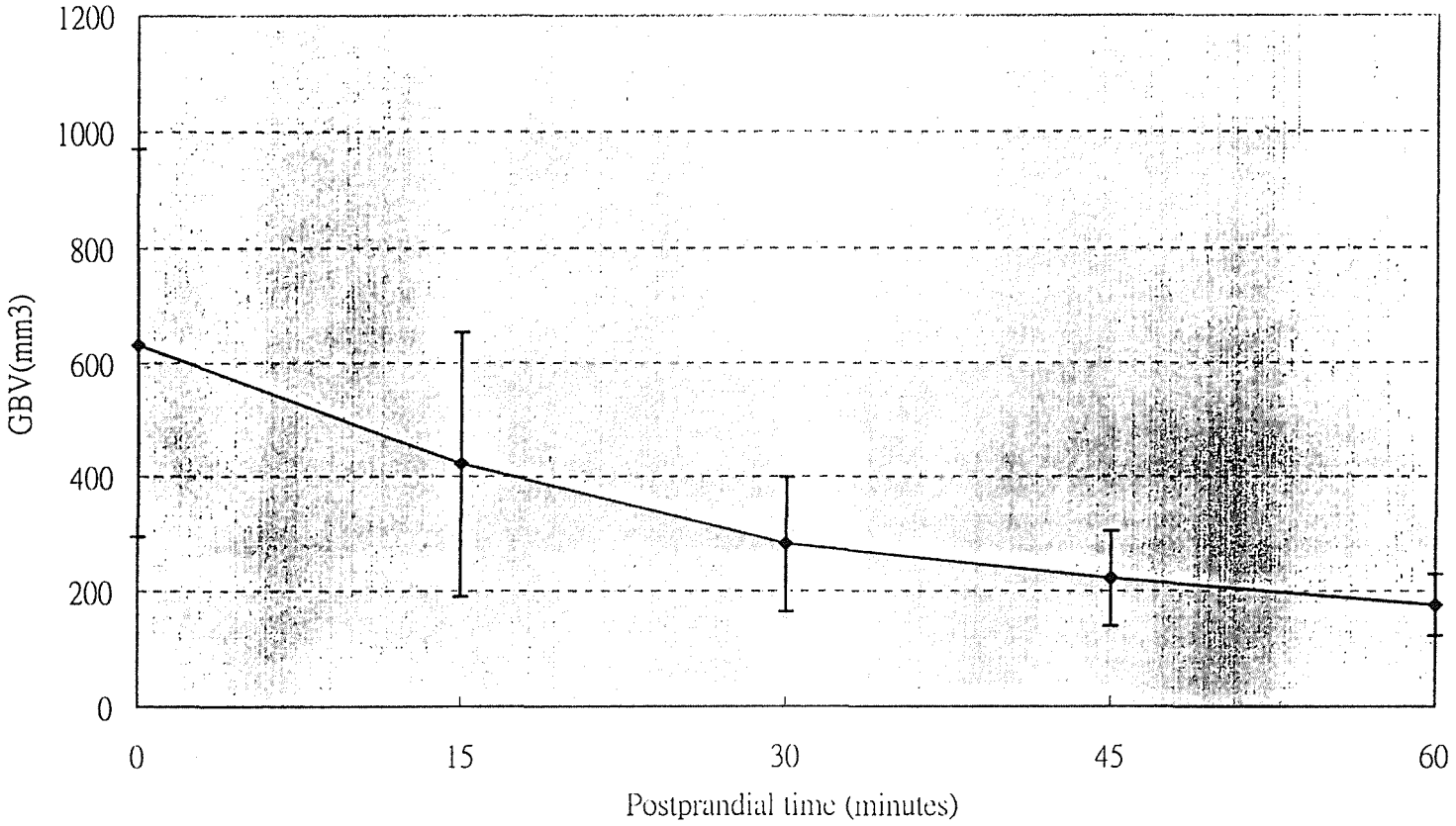

Fig. 3. Relationship of variation in gallbladder contractility to body weight in preterm neonates. Inferior postprandial gallbladder contraction showed in lower body weight, esprcially bellow 1.3 Kg. (r=0.5096, 0.5073, 0.4552, for 30, 45, and 60-minute)

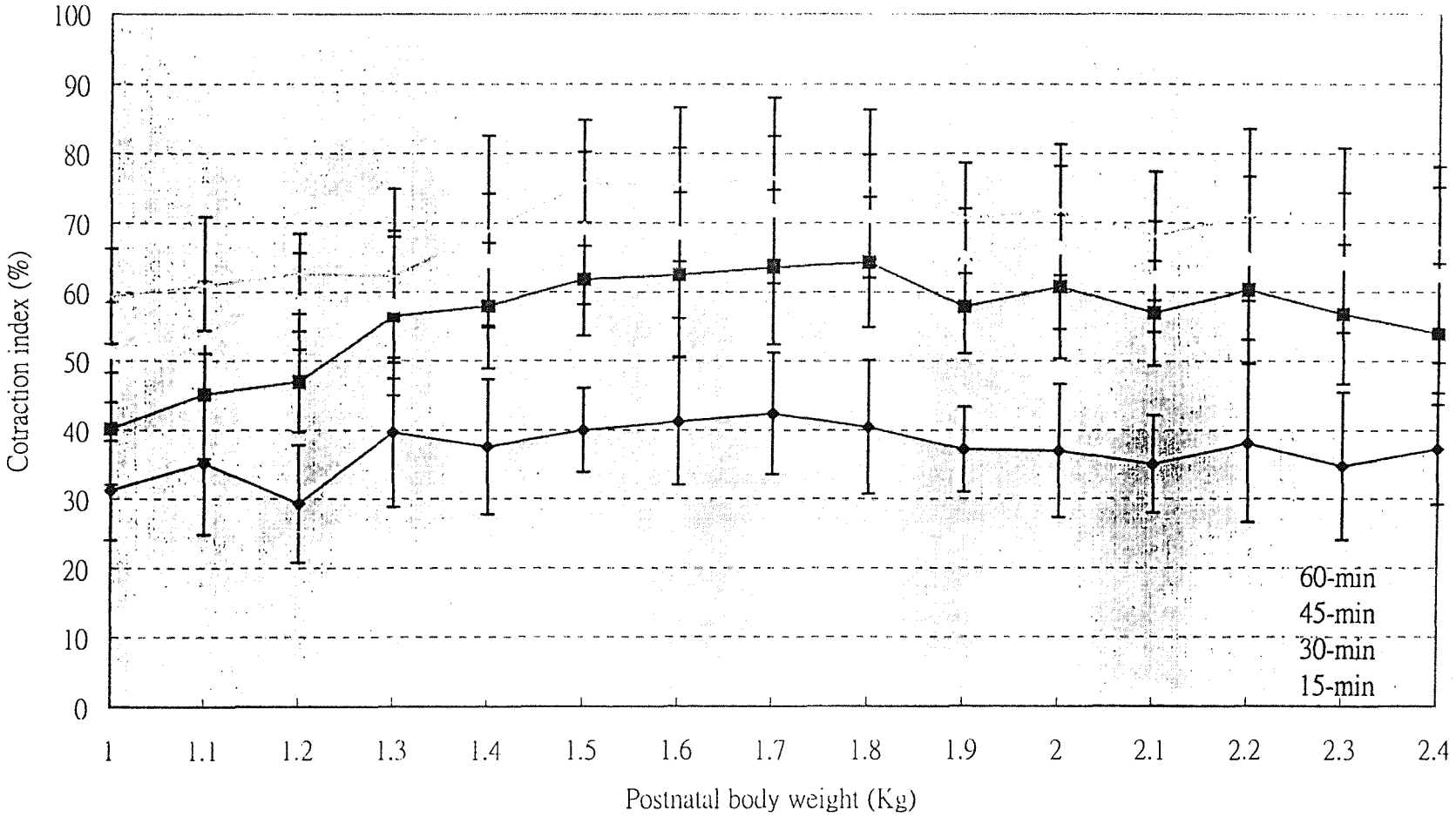

Fig. 4. Postconceptional changes of gallbladder contractility in preterm infants. Postconceptional age dependent difference is significane and poor postprandial cotraction is noted below 32 weeks. (r=0.8902, 0.8203, 0.8048, for 30, 45 and 60-min)