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Congenital diaphragmatic hernia: antenatal prognostic factors

Does cardiac ventricular disproportion in utero predict outcome and pulmonary hypoplasia?

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Abstract Despite regular progress in neonatal intensive care, congenital diaphragmatic hernia (CDH) diagnosed antenatally is still associated with up to 80 % mortality. It is impossible to predict which fetus with CDH will survive or not.
Objective: To identify reliable antenatal predictors of outcome and of pulmonary hypoplasia (PH) in fetuses with CDH.
Design: Retrospective study.
Setting: Paediatric intensive care unit of a university children's hospital.
Patients and methods: Antenatal parameters and presence of left ventricular hypoplasia in utero were compared retrospectively to outcome and to presence of PH in 32 consecutive newborn infants with antenatally diagnosed CDH. Antenatal parameters included: gestational age at diagnosis, herniated organs, associated malformations and presence of polyhydramnios. Size of the cardiac ventricles, the aorta (Ao) and the pulmonary artery (PA) were obtained by fetal echocardiography, from which we calculated a cardioventricular index (left ventricle/right ventricle, LV/RV) and a cardiovascular index (Ao/PA). Delivery was planned in order to provide ventilatory and hemodynamic management. In case of death, PH was assessed according to the following criteria: the lung weight/body weight index and the radial alveolar count. For statistical comparisons, patients were separated into two groups: the hypoplasia group (H) and the non-hypoplasia group (NH).
Results: Thirty-two pregnancies were delivered. Twenty-six newborns died (81 %), 6 survived (19 %). When comparing non-survivors to survivors, predictors of poor outcome were: mean gestational age at diagnosis (23 vs 28 weeks, $p = 0.002$), intrathoracic stomach (20 vs 1 s, $p = 0.01$) and associated malformations (6 vs 0). Cardiac ventricular disproportion, expressed by the LV/RV ratio, appeared to correlate well with a poor outcome (0.63 in non-survivors vs 0.93 in survivors, $p = 0.03$) and with PH (0.63 in the H group vs 0.95 in the NH group, $p = 0.03$).
Conclusions: Our study confirmed the factors for a poor prognosis associated with CDH previously described in the literature, but none with a consistent demonstration of accuracy. LV hypoplasia may be a more accurate predictor of outcome and of PH but it has to be assessed by prospective studies with larger samples. Further basic science and Doppler-flow studies may be helpful to understand the natural history and pathophysiology of LV hypoplasia in CDH.

Key words Congenital diaphragmatic hernia · Ventricular hypoplasia · Pulmonary hypoplasia · Outcome · Antenatal diagnosis

Introduction

Despite advances in perinatal and neonatal intensive care, the mortality from congenital diaphragmatic hernia (CDH) remains high [1–5]. Apart from associated malformations [6–9], the prognosis depends on pulmonary hypoplasia (PH), including anatomical and functional anomalies of the parenchyme and the vasculature [10–17]. Since the advent of antenatal echography in 1980, numerous studies have tried to establish antenatal predictors of outcome [4, 5, 18–20]. However, antenatal echographic assessment of fetal lung volume is technically difficult. Other predictors of a dismal prognosis have been identified but none with a consistent demonstration of accuracy [4, 5, 18–20]. Although in a study published in 1984, autopsy reports from CDH patients showed that they have smaller left-sided cardiac structures [21], only recent evidence from basic science and ultrasound studies strongly suggests that patients with CDH have an underdeveloped left ventricle [22, 23].

The purpose of this study was to identify the value of an underdeveloped left ventricle in predicting outcome and PH in patients with CDH diagnosed antenatally.

Patients and methods

Prenatal management

Forty cases of CDH with an antenatal diagnosis between 1988 and 1994 were retrospectively studied. The pregnancies were followed up either from the beginning in our tertiary care centre, or initially in another hospital and then referred to our institution for further assessment and perinatal management. Each fetus was subjected to a complete anomaly scan.

Morphological echography was always performed by the same physician (E. V.). The diagnosis of CDH was made from a sagittal and transverse cross section of the fetal trunk at the thoracoabdominal level by establishing the presence of abdominal viscera in the thorax and/or a contralateral shift of the heart or the mediastinum. Once the diagnosis was made, a detailed evaluation was made of the nature of the herniated organs (especially stomach and liver), evidence of other congenital malformations and amniotic fluid volume. Polyhydramnios was defined as a large pocket of fluid of 8 cm or more. Values between 5 and 8 cm were defined as an "excess" of amniotic fluid. Fetal echocardiography was performed by the same physician (A. A.). The size of the left (LV) and right ventricles (RV) was measured on a four-chamber view at the level of the ventricle annulus. The aorta (Ao) and the pulmonary artery (PA) were also measured at the level of their annuli. With these data, we established a cardioventricular index: LV/RV, and a cardiovascular index: Ao/PA.

Karyotyping was systematically performed with amniocentesis or fetal blood samples.

This evaluation was followed by a multidisciplinary discussion involving obstetricians, geneticists, echographers, neonatologists and surgeons. A consensus decision was obtained concerning the pregnancy. Interruption of the pregnancy was proposed to the family in the case of karyotyping anomalies and/or lethal anomalies associated with the diaphragmatic hernia. Interruption of pregnancy was never proposed in the case of an isolated diaphragmatic hernia.

Postnatal management

All deliveries were performed at the Children's Hospital Robert Debré with planned neonatal resuscitation in the delivery room, nasal intubation and immediate transfer to the paediatric intensive care unit for pre-operative stabilisation. All patients were managed by mechanical ventilation, volume loading, sedation (midazolam or fentanyl) and paralysis (vecuronium), when necessary.

Mechanical ventilation was performed with a Servo 900C for infants admitted before December 1991 and with high frequency oscillatory ventilation (OHF 1, Dufour, France) after 1991. Persistent pulmonary hypertension was managed by volume loading, catecholamines and prostacyclin until 1993, when nitric oxide was available. Indications for veno-arterial extracorporeal membrane oxygenation (ECMO) varied over time. Until February 1992, ECMO was started in the absence of the usual contraindications and for all patients who did not respond to conventional therapy according to the criteria of Bartlett et al. [24]. Since February 1992, published [13, 14] and personal experiences led us to consider that poor blood gas values, despite maximal therapy [(best partial pressure of oxygen in arterial blood (PaO_2) below 100 mmHg and best partial pressure of carbondioxide in arterial blood ($PaCO_2$) above 40 mmHg], would be associated with a poor prognosis, with or without ECMO. However, for ethical reasons, 80 mmHg for the best preductal PaO_2 and 60 mmHg for the best $PaCO_2$ were the values considered to make ECMO necessary. Patients not fulfilling those criteria were not offered ECMO.

Surgery

Patients underwent surgical repair only after stabilisation had been achieved, whether after conventional therapy or after successful weaning from ECMO.

Anatomical and histological studies

Patients who died underwent a post-mortem examination after parental consent was obtained. After looking for associated malformations, PH was assessed on two criteria [25, 26]. (1) The lung weight to body weight ratio (LW/BW) was the major criteria. PH was considered as certain and major with an LW/BW ratio below 0.009, probable with a LW/BW ratio between 0.009 and 0.018 and absent if the ratio was above 0.018. (2) The radial alveolar count (RAC), as assessed by morphometric methods, is the average of the ipsilateral and contralateral radial alveolar counts. In practice, a line was drawn from the centre of each respiratory bronchiole to the nearest connective tissue septum at right angles to the epithelium, and the number of alveoli were counted.

Severe PH is easy to diagnose at necropsy from the LW/BW ratio alone. However, because lesser or borderline PH is more difficult to establish and because possible overestimation of the lung weight (pulmonary edema, major pulmonary haemorrhage), RAC was also used in uncertain cases after assessement of the LW/BW ratio. Severe PH was confirmed when RAC was less than 3.1.

Table 1 Associated malformations identified at post-mortem examination among children with CDH diagnosed antenatally

Associated malformations	Number of cases
Hypoplastic left-heart syndrome	1
Aortic coarctation	1
Multiple complex cardiovascular anomalies	1
Pulmonary adenomatosis	1
Urinary tract dilatation	2
Ureteropyelic junction obstruction	1
Horseshoe kidney	1
Polyendocrinopathy	1
Fryns syndrome	2
Marfan syndrome	1
Cornelia de Lange syndrome	1

Statistical analysis

Results are expressed as mean ± standard deviation or as proportions. For categorical data, the chi-square test, with continuity correction as appropriate, was used to determine the significance of the difference between two independent groups. The unpaired *t*-test was used to compare continuous data between groups (died vs survived or hypoplasia vs non-hypoplasia; survivors were included among patients without hypoplasia). A two-way analysis of variance with one grouping factor (died vs survived) and one-within factor (before 25 weeks' gestation, after 25 weeks) was used to test grouping, time and interaction effects (time × group). Pearson's correlation coefficient was used to measure the closeness of the relationship between LV/RV and Ao/PA ratios. All *p*-values were two-tailed and considered significant when probabilities were less than 0.05.

Results

Antenatal findings

Termination of pregnancy was proposed in 1 case of interruption of the aortic arch but was refused by the parents for religious reasons. Elective interruption of pregnancy was decided for 8 pregnancies because of the association with karyotypic (n = 3, monosomy 4P, trisomy 13, Turner syndrome) or morphological anomalies (n = 5, 2 Fryns syndrome, 1 Walker-Warburg syndrome, 2 facial anomalies with neck hygroma).

Thirty-two pregnancies (20 boys and 12 girls) were brought to term. The mean age of the mothers was 28.7 years (range 20–38 years). A family history existed in 3 cases: consanguinity, Marfan syndrome and in one couple the mother had an in situ carcinoma of the cervix and the father testicular carcinoma.

Six fetuses had 8 associated anomalies: 2 polycystic kidneys, 2 neck hygromas, 1 interruption of the aortic arch, 1 aortic coarctation, 1 hydrocephalus, 1 talus feet.

The antenatal echocardiographic findings are summarized in Table 2.

Postnatal management

The delivery was always planned. All infants except 1 were full term. The details of the events at birth are given in Table 3. One infant died in the delivery room despite immediate resuscitation. The remaining 31 patients were admitted to the paediatric intensive care unit for pre-operative stabilisation. Three patients responded to conventional therapy alone and survived. In the other 28, values for alveoloar-arterial oxygen gradient and oxygenation index met the classical criteria for ECMO. Fourteen patients were treated with ECMO, 4 of them were operated on and 3 survived. Eleven patients died under ECMO. ECMO was rejected for 14 patients: 4 had multiple lethal malformations, 2 experienced acute deterioration and died before ECMO could be started and in 8 the best blood gas readings were considered too poor according to our protocol (best PaO_2 < 80 mmHg or best $PaCO_2$ > 60 mmHg).

Anatomical and histological findings in non-survivors

Post-mortem examination was refused by the parents of 3 patients: 1 died immediately in the delivery room (the infant with interruption of the aortic arch), 1 had very poor blood gases (best PaO_2 31 mmHg, best $PaCO_2$ 72 mmHg) and died shortly after birth and 1 had better blood gases (best PaO_2 100 mmHg, best $PaCO_2$ 24 mmHg) but died, despite ECMO therapy, of iatrogenic disease. Twenty-three anatomical and histological studies were performed, 22 were complete (necropsies) and one did not include a post-mortem examination but only multiple transthoracic biopsies for RAC evaluation.

Thirteen associated malformations were found at post-mortem examination in 10 patients (Table 1).

For the 21 patients with hypoplasia, the mean LW/BW ratio was 0.01 ± 0.006 (0.003–0.025) and mean RAC 2.55 ± 0.59 (1.7–4.45). Although lung weight was considered to be overestimated in 10 patients because of pulmonary oedema, there was a good correlation between LW/BW ratio and RAC (r = 0.8, p = 0.0001, see Fig. 1). However, in 21 patients with hypoplasia the mean LW/BW ratio was 0.009 ± 0.004 (values < 0.009 are considered to show major PH) [25, 26], and mean RAC was 2.4 ± 0.36, whereas in 2 non-hypoplastic patients these values were, respectively, 0.024 ± 0.002 and 4 ± 0.63.

Comparison of the antenatal findings in survivors and non-survivors (Table 2)

Non-survivors had an earlier diagnosis of CDH (before 25 weeks of gestation: 20 vs 0), more associated malformations and the stomach was found in the thorax more often (20 vs 1). LV/RV ratio and Ao/PA ratio were eval-

Table 2 Comparison of antenatal findings in non-survivors and survivors among 32 patients with CDH diagnosed antenatally. Values are numbers or mean ± SD (*NS* not significant)

	Non-survivors ($n = 26$)		Survivors ($n = 6$)		p
Gestational age	23 ± 4.7		28.1 ± 3.54		0.002
At diagnosis (weeks) < 25 weeks	$n = 20$		$n = 0$		0.0005
Hydramnios	$n = 2$		$n = 0$		NS
Herniated organs					
Stomach	$n = 20$		$n = 1$		0.01
Liver	$n = 3$		$n = 1$		NS
Stomach + liver	$n = 3$		$n = 2$		NS
Echographic anomalies	$n = 6$		$n = 0$		NS
Echocardiography at gestational age (weeks)	21–30 (a)	31–40 (b)	21–30 (a)	31–40 (b)	
LV/RV	0.75 ± 0.15 ($n = 11$)	0.63 ± 0.12 ($n = 16$)	0.89 ± 0.16 ($n = 2$)	0.93 ± 0.17 ($n = 5$)	(a) NS (b) 0.03
Ao/PA	0.81 ± 0.14 ($n = 11$)	0.73 ± 0.13 ($n = 16$)	0.84 ± 0.87 ($n = 2$)	0.95 ± 0.13 ($n = 5$)	(a) NS (b) 0.04

Table 3 Perinatal data for 32 infants. Values are mean ± SD

Vaginal delivery	$n = 28$ (87.5 %)
Caesarean delivery	$n = 4$ (12.5 %)
Mean gestational age (weeks)	39 ± 1.4
Mean birthweight (g)	3044 ± 573
Mean Apgar score at 1 min	4.1 ± 2.6
Mean Apgar score at 5 min	6.4 ± 2.5
Cardiorespiratory arrest at birth	$n = 10$ (31.3 %)

uated at two periods: between 21 and 30 and 31 and 40 weeks of gestation. LV/RV ratio had a tendency to decrease in non-survivors, whereas it rose in survivors (Fig. 2A). This was related to a slowing down of LV growth in non-survivors vs survivors rather than to faster growth of the RV, which showed the same kinetics of growth in both groups (Fig. 2B and 2C). Ao/PA ratio remained constant in non-survivors but seemed to increase in survivors. This was due to a slowing of aortic growth. Therefore LV/RV ratio and Ao/AP ratio were lower in non-survivors. This difference was statistically significant between 31 and 40 weeks of gestation (0.63 vs 0.93 for the LV/RV ratio, $p = 0.03$ and 0.73 vs 0.95 for the Ao/PA ratio, $p = 0.04$).

Comparison of the antenatal findings in patiens with hypoplasia and those without hypoplasia patients (Table 4)

Patients with hypoplasia had an earlier diagnosis of CDH. The nature of the herniated organs had no significace, but in 15 patients the stomach was in the thorax vs 3 in other group. LV/RV ratio and Ao/AP ratio were lower in patients with hypoplasia. This difference was statistically significant between 31 and 40 weeks of gestation for the LV/RV ratio (0.63 vs 0.95, $p = 0.03$).

The decrease in LV/RV ratio was still related to growth slowing of the LV in patients with hypoplasia, while the RV showed normal growth (Fig. 3).

There was a good correlation between LV/RV and Ao/AP ($r = 0.5$, $p = 0.003$; Fig. 4).

Discussion

Despite regular progress in neonatal intensive care, antenatally diagnosed CDH remains associated with a high mortality of 40 to 80 % [1–5]. The pathophysiology of this malformation is complex and includes pulmonary hypoplasia with parenchymal and vascular anomalies associated with anatomical and also functional disorders [10–17]. Several attempts to define reliable antenatal predictors of outcome have been made, but so far none of them have allowed accurate prediction of which fetus with CDH will survive [4, 5, 18–20]. In order to identify risk factors and predict more accurately the outcome of CDH, we analysed retrospectively the evolution of 32 patients with CDH managed in the same institution during pregnancy and after birth.

Our study confirmed the pejorative significance of some predictors previously described in the literature, such as the early diagnosis, the presence of the stomach in the thorax and the existence of associated malformations [4–9, 19, 20, 27, 28]. Actually, all survivors were diagnosed after 25 weeks of gestation. However, 6 infants with an antenatal diagnosis after 25 weeks died. Twenty newborns had the stomach in the thorax and died, but one survived despite this. Therefore none of these criteria can be used to predict severe PH and to propose termination of pregnancy.

In our study, hydramnios was not associated with an adverse outcome (62.5 %, i.e. 20/32 of the records were retrospectively available). However, these find-

Table 4 Comparison of antenatal findings in patients with (H) and without (NH) pulmonary hypoplasia among 29 patients with CDH diagnosed antenatally

	H (n = 21)		NH (n = 8)		p
Gestational age	22 ± 3.6		29.6 ± 4.3		0.0004
At diagnosis (weeks) < 25 weeks	n = 17		n = 0		0.0001
Hydramnios	n = 1		n = 1		NS
Herniated organs					
Stomach	n = 15		n = 3		NS
Liver	n = 3		n = 1		NS
Stomach + liver	n = 3		n = 2		NS
Echocardiography at gestational age (weeks)	21–30 (a)	31–40 (b)	21–30 (a)	31–40 (b)	
LV/RV	0.74 ± 0.18 (n = 8)	0.63 ± 0.13 (n = 13)	0.82 ± 0.08 (n = 5)	0.95 ± 0.17 (n = 8)	(a) NS (b) 0.03
Ao/PA	0.79 ± 0.14 (n = 8)	0.74 ± 0.12 (n = 13)	0.87 ± 0.06 (n = 5)	0.90 ± 0.17 (n = 8)	(a) NS (b) NS

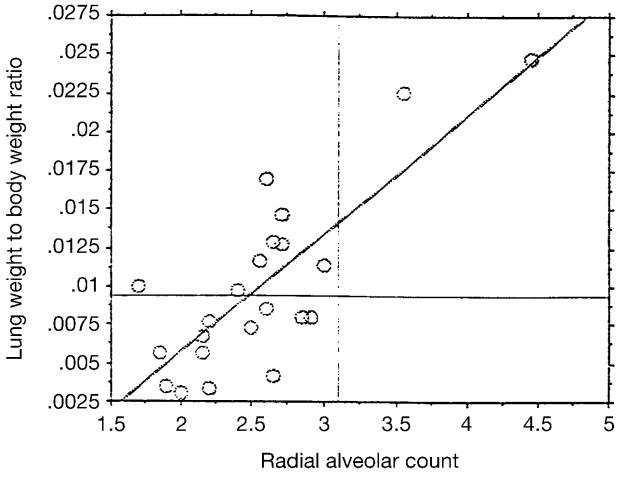


Fig. 1 Correlation of two methods of assessment of pulmonary hypoplasia: lung weight/body weight ratio (LW/BW) and radial alveolar count (RAC). The equation for the regression line is: y = 0.008x–0.01. Correlation is significant with r = 0.8 and p = 0.0001. The horizontal line represents the 3.1 limit for the RAC and the vertical line represents the 0.009 limit for LW/BW ratio. Values below those limits are indicative of severe pulmonary hypoplasia

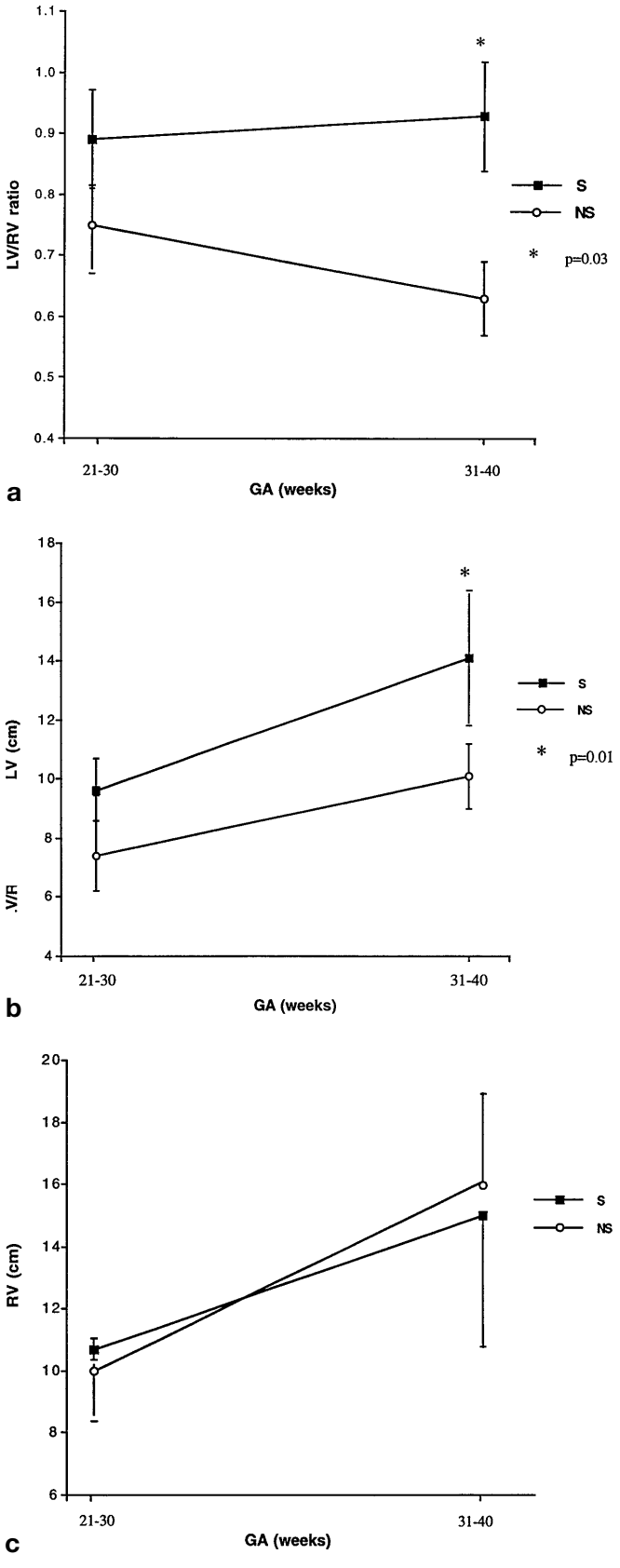
ings are not contradictory to the literature. In fact, the prognostic value of hydramnios is controversial. Adzick and co-workers found in two successive studies that hydramnios predicts a poor prognosis when associated with CDH [4, 19]. Conversely, three other authors found no significance for hydramnios in CDH [8, 29, 30].

Concerning the detection of associated malformations, four lethal malformations were not diagnosed in utero. However, in retrospect, it appeared that in these patients the presence of minor anomalies at fetal echography should have suggested a search for more severe anomalies, since, for example, 2 patients with neck hygroma had, respectively, Marfan syndrome and Fryns syndrome.

Apart from associated malformations, the prognosis of CDH seems to depend on PH. No reliable antenatal predictor of PH in CDH has yet been established. The ratio of fetal thoracic circumference to abdominal circumference is not useful in CDH [31, 32]. An interesting index of PH may be the lung-thorax transverse area ratio. Kamata et al. found a correlation between this index and fetal outcome, but did not confirm PH by morphometric studies [33]. In our study, PH was assessed by the LW/BW ratio and RAC, as described by Askenasi and Perlman [25]. The presence of PH was associated with an early diagnosis and with the existence of ventricular disproportion (Table 4). Patients with hypoplasia had a significantly earlier diagnosis than patients without hypoplasia and no patients in the latter group had an antenatal diagnosis before 25 weeks. Nevertheless, 4 patients with PH were diagnosed after 25 weeks.

The most significant finding was that LV hypoplasia may predict outcome and PH. Taking lung measurements in utero is difficult, i. e. PH is difficult to assess before birth. Furthermore, it has been shown that cardiac weight can predict lung weight in fetal lambs with a surgically created diaphragmatic hernia [34]. So cardiac measurements may be an indirect indication of lung hypoplasia. Our results showed a positive relationship between sonographic LV/RV ratio and PH assessed by morphometric studies. Obviously, these data have to be confirmed by a prospective study with more patients.

Ventricular disproportion appeared as a dynamic process, since the LV seemed to stop growing especially in the last few weeks of gestation, whereas the RV continued to grow. It may explain why the lower LV/RV ratio in non-survivors and in patients with hypoplasia was statistically significant only between 31 and 40 weeks of gestation. Additionally, a larger sample would have given more power to this parameter.



The contribution of the cardiovascular system in the pathophysiology of CDH has been largely ignored in the literature [35]. Nevertheless, previous post-mortem reports from patients with CDH have shown that in human newborns with CDH the left ventricle, interventricular septum and atria are smaller than those in age-matched controls [21]. Schwartz et al. showed that the LV mass index, assessed by two-dimensional echocardiography, is diminished in newborns with CDH [22]. More recently, Glick and co-workers performed anatomical and biochemical studies of the heart in the CDH-lamb model using the DNA/protein ratio. Decreased weight of the LV in CDH-lambs and identical DNA/protein ratio of the LV in both CDH and littermate controls implied that this underdevelopment of the LV is due to left ventricular hypoplasia and not to atrophy and that this hypoplasia is different from congenital hypoplastic left-heart syndrome [23]. Other authors have shown that ventricular disproportion assessed by fetal echocardiography is associated with poor outcome, as confirmed by our study [30, 36]. LV hypoplasia, associated with pulmonary hypoplasia, may be the missing link in the pathophysiology of CDH [37, 38].

The aetiology of LV hypoplasia remains unknown. Some have suggested that herniated organs were causing mechanical compression of the heart [21]. Another explanation could be altered hemodynamics. As the development of the heart chambers depends on the blood flow they receive, decreased LV flow in utero could cause LV hypoplasia. Diminished pulmonary venous return due to lower pulmonary blood flow by pulmonary vessel hypoplasia is unlikely to cause LV underdevelopment because only 8–10 % of cardiac output goes through the lung [39]. A more satisfying explanation would be decreased flow across the patent foramen ovale, as suggested by decreased a Ao/PA ratio. Increased left atrial pressure by rotation of the heart in the chest and disruption to the relationships between heart structures leads to diminished right-to-left shunting through the foramen ovale, increases PA pressure and flow, thus increasing PA and patent ductus arteriosus diameters [21, 22]. Examination of fetal cardiac blood flow by determining velocity waveforms at the level of the atrioventricular valves could provide information about afterload, preload and ventricular compliance as shown in fetuses of insulin-dependant diabetic mothers [40]. Furthermore, if one accepts that

Fig. 2 Left ventricular (LV) and right ventricular (RV) growth through gestational age *GA*, weeks 21 to 30 and 31 to 40 in survivors (S) versus non-survivors (NS). **a** Evolution of LV/RV ratio: LV/RV ratio decreased in non-survivors, whereas it rose in survivors ($p = 0.03$). **b** LV grew significantly more in survivors than in non-survivors ($p = 0.01$). **c** Growth kinetics of RV was the same in both groups

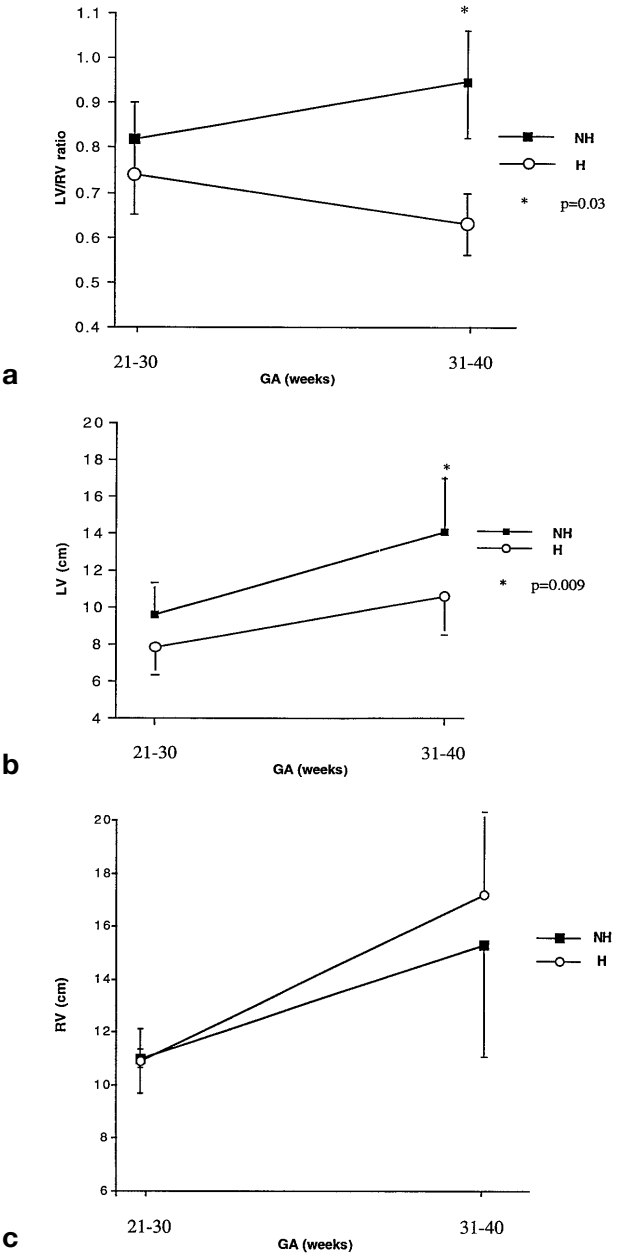


Fig. 3 Left ventricular (LV) and right ventricular (RV) growth through gestational age *GA*, weeks 21 to 30 and 31 to 40 in patients with pulmonary hypoplasia (H) versus patients without pulmonary hypoplasia (NH). **a** Evolution of LV/RV ratio: LV/RV ratio decreased in H patients, whereas it was stable in NH patients ($p = 0.03$). **b** LV grew significantly more in NH patients than in H patients ($p = 0.009$). **c** Growth kinetics of RV was the same in both groups

PH is not only the consequence of a defect of the diaphragm but primarily an abnormal development of the mesenchyme [41], one cannot exclude that LV hypoplasia is a part of this abnormal development during fetal life.

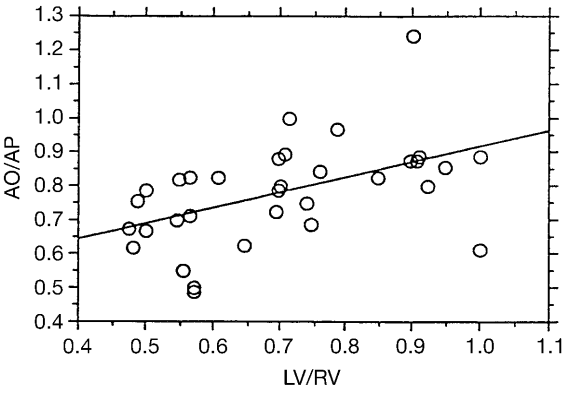


Fig. 4 Correlation of aortic/pulmonary artery ratio *Ao/PA* and left/right ventricle ratio *LV/RV* in survivors and non-survivors. The equation for the regression line is: $y = 0.45x + 0.46$. Correlation is significant with $r = 0.5$, $p = 0.003$

In addition, structural heart anomalies could sustend the pathophysiology of CDH and explain cardiac dysfunction. Actually, in CDH infants who eventually die we found that the LV have a "cone-shaped" morphology (unpublished data). An interesting aspect would be the study of the ultrastructure and the disposition of the myocardial fibres [42]. This could have an impact on the management of infants with CDH. Traditionally, one of the strategies in the treatment of persistent pulmonary hypertension is volume loading to elevate systemic blood pressure above pulmonary pressure. But maybe it does more harm to a hypoplastic, non-compliant left ventricle.

In conclusion, we showed that ventricular disproportion may be a good predictor of death and of pulmonary hypoplasia assessed by histological studies. Prospective studies with larger samples are needed to confirm our results. LV hypoplasia could be the "missing link" in the pathophysiology of CDH and may account for a part of the hemodynamic disruption in the newborn with CDH [43]. Prospective studies with larger samples are necessary to determine whether ventricular disproportion is a reliable prognostic indicator in CDH. In addition, examination of fetal cardiac blood flow and ultrastructural studies of the heart will enhance our knowledge of the mechanism regulating the growth and function of the developing heart.

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