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# Congenital diaphragmatic hernia – the past 25 (or so) years

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I would like to thank the Canadian Association of Pediatric Surgeons for the honor of the invitation to give the annual McLeod Lectureship. It has been a distinct pleasure for both Pam and me to attend our first CAPS meeting, and I can assure you it will not be our last. I would also like to thank Dr. Peter Fitzgerald for the hospitality and Dr. BJ Hancock for making all of the arrangements.

As I will discuss, I became interested in congenital diaphragmatic hernia (CDH) a number of years ago. I think it is important to keep in context that CDH is largely a problem being faced in developed nations. Lower- and middle-income countries frequently will not have the resources nor would it necessarily be appropriate to dedicate the resources necessary to care for some of these infants. CDH occurs in approximately 1 in every 2400 live births. Current mortality rates are approximately 30%. However, this accounts for almost 1% of the entire US infant mortality. In a manuscript several years ago, the estimated cost for caring for a CDH was published [1]. If we adjust inflation to 2015 dollars, we would estimate that CDH would be responsible for just less than $800,000,000 in US costs in 2015 alone. Importantly, this would just represent hospital costs and not the growing expense necessary to care for some of these infants after discharge. That makes CDH, while uncommon, a very deadly and very expensive disease to manage. Hence, a better understanding of the cause and best treatments are important.

CDH has been described for a number of centuries, but it was Vincent Bochdalek's report in the 1800's describing two infants who died at birth with a posterolateral diaphragmatic hernia that led to his name being appended to the typical diaphragmatic hernia that we will be talking about today. For a number of years it was assumed that CDH was because of a failure of the closure of the pleuroperitoneal canals. However, some experimental work in the last two decades has demonstrated that this is clearly not the case. Dr. John Greer and colleagues have done a series of experiments using the nitrofen herbicide model of diaphragmatic hernia in the rat. What they have demonstrated is the pleuroperitoneal fold (PPF), which is a mesenchymal structure seen early in development, is impacted in the nitrofen-treated animals [2]. It is failure of development of the PPF that leads to a defect in this mesenchyme. Migrating muscle precursors are then unable to locate onto the absent substratum. In an elegant manuscript in 2015, Merrell and colleagues also demonstrated that the PPF appears to be responsible for the majority of if not the entire muscular diaphragm [3]. The PPF has been seen on some human embryo specimens as well. Thus, it appears that defects in the PPF are the likely culprits in the development of CDH. Both experimental and genetic data would also suggest that defects in the retinoic acid pathway, which appears to be critical in diaphragm development, are likely important in formation of CDH.

The major clinical problems that we are faced with in managing an infant with CDH are the hypoplastic lungs and pulmonary hypertension. A series of postmortem studies demonstrated that not only is the involved side hypoplastic, but the contralateral side is also abnormal. Reid and colleagues described significant muscularization of the pulmonary arteries in infants with CDH some time ago, and others have confirmed this [4]. This is likely contributory to the significant pulmonary hypertension seen in these infants. Indeed long term, it is effective management of the pulmonary hypertension that remains one of the major challenges that we face today.

For our discussion, we can start in January 1987. An infant was transferred to the Children's Hospital Los Angeles where I was a senior fellow. The infant had a typical left-sided CDH and was rushed to the operating room for emergent surgery. Following operation the infant developed worsening respiratory distress and was placed on extracorporeal

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membrane oxygenation (ECMO). This was the first infant placed on ECMO at CHLA, and this began my journey with CDH. If you look at management of CDH in 1987 (Table 1), emergency operation was considered standard of care. ECMO and hyperventilation were used, and many of the current therapies were simply unavailable. Long-term follow up was felt not to be needed, and overall survival was 50%. To put that in historical context, the Canadian Prime Minister at the time was Brian Mulroney and the US President Ronald Reagan was in his second term. It is interesting that the Simpson's cartoon was also introduced in 1987.

## 1. Timing of operation

In 1987, CDH was felt to be an acute surgical emergency. Indeed, in the surgical textbooks at the time, CDH was felt to be the most urgent surgical emergency in the newborn infant. The rationale behind this was that it was thought that the bowel was causing pulmonary compression and that emergently removing the bowel from the chest would improve the situation. While this may have been true for those type of patients seen in the 1950s, it was not by the late 1980s. Frequently, after the bowel was removed from the chest, the patient would be left with an ex-vacuo pneumothorax and still with a mediastinal shift. The first reports for delayed surgical intervention occurred in 1987 and 1988 by Sakai as well as Langer, both from Sick Children's Hospital, and Hazebroek from the Netherlands [5–7]. Subsequent reports appeared in the early 1990s all talking about the utilization of preoperative stabilization prior to surgical intervention. This very rapidly became an accepted standard, and by 1995 when the CDH study group was founded, only one third of patients underwent surgical correction in the first 24 h of life. Interestingly, less than 5% of patients now undergo surgical repair in the first 24 h. During the same time interval, there was a significant shift in very delayed surgical intervention. The most recent data from the registry shows more than half of the patients with diaphragmatic hernia undergoing surgical repair more than five days of life. Very clearly preoperative stabilization has now become a routine and standard practice.

## 2. Ventilation

Given the fact that many of these infants will have some degree of hypoxemia in the first few hours of life, steps to try and alleviate this would be considered appropriate. In an early manuscript from 1981, Drummond and colleagues demonstrated that with either hyperventilation or alkalosis, they saw a significant shift in the patient's oxygenation because of relaxation of the pulmonary vasculature. While this was known physiology, it was one of the early studies that demonstrated this in humans. However, the data for this report were from six patients, and they only looked at the immediate response and not the impact that hyperventilation might have on lung injury [8]. Despite that, hyperventilation therapies for diaphragmatic hernia rapidly became the standard of care. By the late 1980s, hyperventilation was routine. However, the cost of this was growing evidence of ventilator-associated lung injury. Dr. Jen Wung from Columbia first reported on the use of low pressure ventilation in infants with persisting pulmonary hypertension and then subsequently reported this being used in CDH [9,10]. A series of reports then came out in the late 1990s that survival could be improved by avoiding hyperventilation and using permissive hypercapnia [11,12]. These manuscripts demonstrated that it was the interventions that were leading to some of the deaths that we were seeing in diaphragmatic hernia and gradually led to a frame shift in management. Currently, the overwhelming majority of infants with CDH are managed with a permissive hypercapnia strategy. While this definition does vary from institution to institution, in general it implies limited peak inspiratory pressure to avoid barotrauma with the acceptance of moderate degrees of hypoxemia and hypercarbia.

**Table 1**
Management of CDH – 1987.

| Emergency operation | |
|---|---|
| Hyperventilation | |
| High frequency oscillation | Unavailable |
| Surfactant | Unavailable |
| Fetal interventions | Unavailable |
| ECMO | Used as a rescue therapy. Less than 20 centers |
| Pulmonary hypertension | Treated with Tolazoline |
| Role of the heart | Unknown |
| Long-term follow up | Not needed |
| Overall survival | 50% |

## 3. Fetal surgery

In some early experiments first published in 1980, Harrison and colleagues demonstrated in a lamb model of diaphragmatic hernia that by creating the defect in utero and then mimicking surgical correction in utero as well, they were able to ameliorate the pulmonary hyperplasia seen in this model of CDH [13]. This led to the hypothesis that the pulmonary hypoplasia was potentially reversible if diagnosed in adequate time and corrected in utero. The first report of a successful in utero repair was in The New England Journal of Medicine in 1990, again by Harrison and colleagues [14]. However, with successive attempts, both mortality and morbidity were high, and open repair of CDH with liver herniation was abandoned. The group subsequently published a prospective evaluation of utilization of open fetal repair in infants without liver herniation. However, while feasible, this did not improve the survival in what turned out to be a lower risk group of patients, and this too was abandoned [15]. Wilson reported the use of experimental tracheal ligation using the lamb model in 1993, demonstrating a dramatic improvement in fetal lung growth [16]. Tracheal occlusion can result in expansion in fetal lungs with actual reduction of viscera into the abdomen in cases of CDH. However, it also delays pulmonary maturation and can inhibit surfactant production. This technique was rapidly applied in another prospective trial by the group at UCSF. However, there were significant technical problems using open tracheal occlusion, and survival was quite low. This group then rapidly evolved the technique of using endoscopic approaches with balloon inflation. The balloon itself could then effectively obstruct the trachea leading to lung growth. Following the development of this technique, a randomized trial was performed to evaluate fetal endoscopic occlusion in infants with severe CDH. This trial was closed by the data safety monitoring committee because of lack of difference between the control group and the standard of care group, both with an approximate 75% survival [17]. Following this, interest in fetal intervention for CDH in the US waned. Dr. Deprest and colleagues, however, continue to evolve the technique of endoscopic occlusion in CDH and developed a minimally invasive approach which could ultimately be done under a local anesthesia. Using historical controls, they demonstrated that fetal intervention resulted in a significant improvement in survival, especially in extremely high-risk patients [18]. However, a criticism of this technique has been an ongoing evolution in the post-natal management of patients in Europe. In a manuscript by Van den Hout and colleagues, they demonstrated a marked improvement in survival in European centers after adapting a standardized protocol [19]. Also of concern is the accuracy of the selection criterion for infants to receive fetal tracheal occlusion. As we will discuss shortly, infants with primary repair of CDH are considered a very low-risk group of patients with survival rates exceeding 95%. In a recent report by Ali and colleagues, almost one third of patients who underwent fetal tracheal occlusion had primary repair of the diaphragm, leading to some serious questions about the accuracy of patient selection [20]. Indeed, the most common utilized prenatal predictor, the lung-to-head ratio (LHR), has not been validated across multiple centers.