

Team-based care with early recognition and treatment of cardiac dysfunction for infants with CDH

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Abstract

Objective

Identify how a core congenital diaphragmatic hernia (CDH) team coupled with early recognition and treatment of cardiac dysfunction changed outcomes for infants with CDH.

Methods

A retrospective chart review compared a historical cohort from 2015–2019 ($n = 51$) with a post-guideline cohort from 2020–2025 ($n = 53$). Statistical analysis was performed with Fisher's exact, unpaired t-test, and Mann Whitney U-test.

Results

Survival improved from 68.6% to 88.7% ($p = 0.016$) and ECMO utilization decreased, 51.0% to 26.4% ($p = 0.015$). Infants with cardiac dysfunction had increased survival (47.3% vs. 81.8%, $p = 0.014$) and less ECMO utilization (68.4% vs. 36.3%, $p = 0.043$). Vasoactive choices evolved with dopamine replaced by norepinephrine, low-dose epinephrine, or calcium gluconate. Inhaled nitric oxide (iNO) use in the first 48 hours decreased significantly while prostaglandin E1 (PGE1) use increased.

Discussion

We implemented a core CDH team focused on a generalizable, physiology-driven approach to identify and treat cardiac dysfunction using standard neonatal echocardiography to improve outcomes.

Introduction

Congenital diaphragmatic hernia (CDH) is a congenital anomaly that occurs in approximately 1 in 3000 live births and carries significant cardiorespiratory morbidity and mortality. The etiology of cardiorespiratory failure in CDH is multifactorial, impacted by pulmonary hypoplasia¹, pulmonary hypertension^{2, 3, 4, 5}, and cardiac dysfunction^{6, 7, 8, 9}. Extracorporeal membrane oxygenation (ECMO) utilization remains at nearly 30% for infants with CDH, with ECMO survival of 50%¹⁰. While national survival from large cohort studies has remained stable (70–75%), some individual centers have implemented comprehensive CDH care guidelines with reported improvement in survival to as high as 85%^{10, 11, 12, 13, 14, 15}.

Areas of controversy in the care of infants with CDH include the role of iNO¹⁶, timing of echocardiogram¹³, and the appropriate choice of vasoactive medications in managing systemic and pulmonary vascular

resistance¹⁷. The benefit of conventional treatment with iNO in infants with CDH continues to be questioned. The NINOS trial, while small and with significant methodical challenges, revealed no significant benefits of iNO use and identified an increased need for ECMO in infants with CDH¹⁸. In the interim, many studies that have challenged the role of iNO in infants with CDH have similarly shown an increased mortality in infants who receive iNO without clear benefit^{19,20}. Further, there is increasing recognition of post-capillary pulmonary hypertension, driven by left atrial hypertension in the setting of left ventricular (LV) dysfunction, in addition to the historically recognized pre-capillary pulmonary arterial and arteriolar hypertension in infants with CDH². Most concerning, emerging data demonstrate that isolated LV or combined right ventricular (RV) + LV dysfunction are predictive of high mortality in infants with CDH and the need for ECMO support^{21,22}. These studies promote the use of early diagnostic imaging, limiting the use of iNO in the setting of cardiac dysfunction, and recognizing pre-capillary and post-capillary pulmonary hypertension.

To improve care for infants with CDH, we first identified factors that contribute to disparity in morbidity and mortality: inter-center variability, center volume^{23,24}, and the presence and persistence of LV or RV + LV cardiac dysfunction^{6,7,21,22}. The success of high volume, as well as individual high-performing centers, demonstrates that experience and focus on the complex cardiorespiratory physiology of infants with CDH may optimize outcomes. Therefore, in 2020, our center formed a dedicated CDH team consisting of neonatal intensivists, neonatal nurse practitioners, and pediatric surgeons, with the addition of a dedicated cohort of CDH nurse champions in 2021. The core team developed a comprehensive physiology-driven guideline, implemented geographic co-location within the Neonatal Intensive Care Unit (NICU), and directed all care of infants with CDH. The physiologic guideline focuses on the early identification and treatment of cardiac dysfunction coupled with limitation of iNO use in the setting of LV dysfunction.

This study aimed to characterize the impact of a multi-disciplinary care team in combination with revised physiology-driven resuscitation and care guidelines that concentrate on early recognition and treatment of cardiac dysfunction on our center's clinical outcomes for infants with CDH. Our primary outcomes of interest were survival to NICU discharge, ECMO utilization, and ECMO survival. Secondary outcomes were rates of cardiac dysfunction, changes in vasoactive use, and changes in iNO utilization. We hypothesized that a core team following physiology-driven guidelines would improve outcomes in this complex population.

Methods

1. Study Cohort and Design

This retrospective cohort study included all infants diagnosed with CDH at St. Louis Children's Hospital (SLCH) Level IV NICU from 2015–2025. Data were abstracted from the electronic medical record with IRB approval through Washington University in St. Louis. Prenatal data were obtained, if available, from

all infants with a prenatal diagnosis and an observed-to-expected lung-to-head ratio (O/E LHR) or MRI total fetal lung volume (TFLV) were used to stratify severity. Severe CDH was defined as O/E LHR < 25 or TFLV < 25, moderate CDH as O/E LHR 25–35 regardless of liver position, >35–45 with liver intra-thoracic, or TFLV 25–35, and mild CDH as O/E LHR 35–45 with liver intra-abdominal, > 45 with intra-thoracic liver, or TFLV > 35²⁵. Infants without prenatal data were stratified as mild if the liver was intra-abdominal and moderate if the liver was intra-thoracic.

2. Cohort Delineation and Management

Infants were delineated into two treatment epochs, historical treatment and post-guideline treatment, based on year of admission. Infants admitted to our NICU with CDH from 2015–2019 were placed into the historical cohort and those treated from 2020–2025 were placed into the post-guideline cohort. Infants admitted during the historical cohort epoch were admitted to any available bedspace in the NICU, and treatment was managed by any NICU provider. Historic cohort treatment lacked focus on early recognition or treatment of cardiac dysfunction. Early use of high-frequency oscillatory ventilation (HFOV) and the use of dopamine for hypotension were standard of care during that time. The post-guideline cohort was admitted with geographic cohorting in the NICU and treatment was managed by a single NICU team comprised of a core group of physicians, nurse practitioners, and nurses that followed comprehensive, physiology-driven care guidelines.

3. Comprehensive Care Guideline and Team

A comprehensive care guideline and dedicated CDH team (Fig. 1A) aimed to improve the outcomes of our infants with CDH by mitigating systemic and cultural challenges in the NICU and bridging knowledge gaps through a three pronged approach: 1) a dedicated geographic location of all infants with CDH; 2) a core CDH-specific care team including trained neonatologists, nurse practitioners, and nurses that provide 24-hour coverage for these infants. In addition, a neonatologist on the CDH team attends all deliveries, initial stabilizations, ECMO cannulations, and surgical interventions for infants with CDH.; 3) early focus on diagnosis and treatment of cardiac dysfunction (Fig. 1B). Care is provided collaboratively with our pediatric surgery group.

To address the complex and interrelated etiologies for cardiorespiratory failure in infants with CDH and the significant role of cardiac dysfunction in extra-uterine transition and outcomes^{8, 21, 26}, we revised our institutional guidelines to emphasize timely diagnosis of cardiac dysfunction with early targeted echocardiogram (ECHO) to support early identification and treatment. Under the revised guidelines, early LV or combined RV + LV cardiac dysfunction was managed as outlined in Fig. 1B. The initial and all subsequent ECHOs were read and interpreted by an attending cardiologist, regardless of the time of day the ECHO was obtained. Right ventricular dysfunction was characterized by a qualitative view of the RV along with tricuspid annular plane systolic excursion (TAPSE). Left ventricular systolic dysfunction was characterized by M-mode and fractional shortening.

Further, under the revised guidelines, treatment of cardiac dysfunction utilized inotropes such as low-dose epinephrine (≤ 0.05 mcg/kg/min) and maintenance of the serum ionized calcium level at 5-5.5 mg/dL, reflecting the role of calcium in supporting the function of the neonatal myocardium²⁷. In the setting of RV dysfunction with systemic or supra-systemic RV pressures, we initiated prostaglandin E1 (PGE1) therapy to maintain ductal patency and systemic output^{28,29}. The addition of milrinone could be utilized at ≥ 24 hours of life if cardiac dysfunction persisted. Blood pressure goals were based on physiologic endpoints of perfusion with avoidance of supra-systemic blood pressures. Given the potential additional benefit of reduction in pulmonary vascular resistance (PVR), hypotension was managed with norepinephrine and vasopressin as first and second line vasopressors, respectively^{30,31,32,33}. The use of iNO was avoided in the setting of LV or combined RV + LV dysfunction, unless cardiac dysfunction resolved and pulmonary hypertension persisted. Inhaled prostacyclins (PGI2) were reserved for infants with pulmonary hypertension refractory to other interventions. Long-term management of pulmonary hypertension was preferentially treated with sildenafil with the availability of intravenous PGI2 (treprostinil) for severe cases. Our respiratory strategy utilized first-intention pressure-controlled ventilation and a PEEP of 4 cmH₂O to limit hyperinflation during the initial lung recruitment period. Infants were transitioned to volume-targeted ventilation to maintain functional residual capacity (FRC) to limit pulmonary vasoreactivity^{26,34}. High frequency oscillatory ventilation (HFOV) was utilized as a rescue modality for refractory hypercarbia.

4. Data Collection

Demographic data were collected by retrospective chart review and included gestational age, male sex, birthweight, reported maternal race. Prenatal indices collected were O/E LHR, side of hernia, liver position, and TFLV¹². Birth characteristics were inborn delivery, Apgar scores, mode of delivery, and initial arterial blood gas measurements. An infant was considered inborn if delivered at our primary delivery hospital, Barnes Jewish Hospital Parkview Tower, which is physically connected to our NICU by a bridge.

We report length-of-stay for survivors, surgical repair approach, use of HFOV, overall survival to discharge, ECMO utilization, ECMO survival, and discharge respiratory support. Measures of cardiac dysfunction were determined by echocardiography in the first 24 hours of life, and for the post-guideline cohort we characterize the cardiac function over the first 72 hours of life. We report the use of the following vasoactive infusions in both cohorts: dopamine, norepinephrine, epinephrine, calcium gluconate infusion, and milrinone as well as pulmonary vasodilator therapy with iNO in the first 48 hours of life, iNO during the hospital stay, sildenafil, treprostinil, inhaled prostacyclins, and use of PGE1 therapy.

5. Statistical Analysis

Descriptive statistics were used to characterize baseline data, demographic information, and clinical outcomes for the historical and post-guideline cohorts. Categorical data comparing outcomes between

the two cohorts were analyzed with the Fisher's exact test. Continuous data were analyzed using a Mann Whitney U test and reported as median and IQR. For TFLV and ECMO duration, which were normally distributed between the two cohorts, an unpaired t-test was used, and results were reported as mean and standard deviation. Data were analyzed using GraphPad Prism 10® (Boston, MA). Significance was defined as $p < 0.05$.

Results

1. Baseline Characteristics

A total of 117 infants were identified with 104 infants included for analysis. Eight infants were excluded from the historical cohort: 2 with Trisomy 18, 1 with CDH + giant omphalocele, 1 with Morgagni hernia, and 4 with multiple congenital anomalies where comfort care was pursued by the family. Five were excluded from the post-guideline cohort: 3 with Morgagni hernia, 1 with complex congenital heart disease where comfort care was pursued by the family, and 1 infant with CDH + giant omphalocele. After delineation into treatment epochs, the historical cohort was comprised of 51 infants, and the post-guideline cohort contained 53 infants.

There were no statistical differences in infant birth weight, maternal race, mode of delivery, Apgar scores, intrathoracic liver position, or initial arterial blood gas measurements (Table 1). There was a higher percentage of male infants in the historical cohort with a lower gestational age (39 weeks vs 38 weeks, $p = 0.034$) and trend toward lower O/E LHR (49% vs. 41.7%, $p = 0.053$) in the post-guideline cohort. There was no difference in CDH severity between the two cohorts (Table 1). More infants underwent minimally invasive repair in the post-guideline cohort (9.8% vs. 26.4%, $p = 0.041$) (Table 2) reflecting a change in surgical practice with more surgeons utilizing minimally invasive approaches between the two cohorts rather than a difference in cohort severity. A similar number of infants underwent patch repair, and there was a small decrease in non-repair in the post-guideline cohort (9.8% vs. 3.8%, $p = 0.265$). There was no significant difference in the proportion of infants discharged home on room air, on oxygen by nasal cannula, or with a tracheostomy at time of NICU discharge in either cohort.

Table 1
Cohort characteristics

Variable	Historical Cohort (n = 51)	Post-Guideline Cohort (n = 53)	p-value
Gestational age, weeks, median [IQR]	39 (37–39)	38 (36–39)	0.034
Male sex, n (%)	43 (84.3)	30 (56.6)	0.003
Birthweight, grams, median [IQR]	3080 (2800–3470)	3130 (2555–3387)	0.649
Left CDH, n (%)	47 (92.2)	45 (84.9)	0.359
Intrathoracic liver, n (%)	25 (49.0)	25 (47.2)	1
O/E LHR, %, median [IQR]	46.5 (34.3–64.8)	40.0 (32.0–48.3)	0.053
TFLV, %, mean (SD)	30.41 (14.5)	35.55 (21.1)	0.249
APGAR 1 min, median [IQR]	4 (2–7)	4 (1–7)	0.778
APGAR 5 min, median [IQR]	7 (5–8)	7 (5–8)	0.961
First pH, median [IQR]	7.21 (7.09–7.31)	7.17 (7.02–7.27)	0.183
First paO2 mmHg, median [IQR]	64.0 (44.0–125.0)	55.0 (45.5–75.0)	0.268
First pCO2 mmHg, median [IQR]	62.5 (46.0–86.0)	68.0 (52.5–91.5)	0.469
Vaginal delivery, n (%)	34 (66.7)	35 (66.0)	1
Inborn, n (%)	40 (78.4)	38 (71.7)	0.500
Maternal ethnicity, n (%)			
White	41 (80.4)	47 (88.7)	0.285
Black	6 (11.8)	5 (9.4)	0.758
Hispanic	3 (5.9)	1 (1.9)	0.358
Asian	1 (1.9)	0 (0)	0.49
CDH severity, n (%)			
Mild	23 (45.1)	19 (35.8)	0.425
Moderate	12 (23.5)	19 (35.8)	0.202
Abbreviations: IQR = interquartile range, CDH = congenital diaphragmatic hernia, O/E LHR = observed-to-expected lung-to-head ratio, SD = standard deviation, TFLV = total fetal lung volume, min = minute, ECMO = extracorporeal membrane oxygenation, echo = echocardiogram			

Variable	Historical Cohort (n = 51)	Post-Guideline Cohort (n = 53)	p-value
Severe	16 (31.4)	15 (28.4)	0.831
Surgical repair approach, n (%)			
Open laparotomy	41 (80.4)	37 (69.8)	0.26
Minimally invasive	5 (9.8)	14 (26.4)	0.041
Patch repair	21 (45.6)	21 (41.2)	0.686
Non-repair	5 (9.8)	2 (3.8)	0.484
Repair on ECMO	20 (76.9)	3 (21.4)	0.002
Time of initial echo, median [IQR]	4 (2.5–11)	2 (2–3)	< 0.001
Number of echos, median [IQR]	3 (1–6)	7 (3–13)	< 0.001
Abbreviations: IQR = interquartile range, CDH = congenital diaphragmatic hernia, O/E LHR = observed-to-expected lung-to-head ratio, SD = standard deviation, TFLV = total fetal lung volume, min = minute, ECMO = extracorporeal membrane oxygenation, echo = echocardiogram			

Table 2
Clinical outcomes of the infant cohort

Variable	Historical Cohort (n = 51)	Post-Guideline Cohort (n = 53)	p-value
Primary outcomes			
Survival to discharge, n (%)	35 (68.6)	47 (88.7)	0.016
ECMO utilization, n (%)	26 (51.0)	14 (26.4)	0.015
ECMO survival, n (%)	11 (42.3)	10 (71.4)	0.104
ECMO duration, days, mean (SD)	21.42 (13.57)	12.6 (6.9)	0.040
Ventilation and nitric oxide, n (%)			
HFOV	30 (58.8)	18 (33.9)	0.018
iNO during hospitalization	38 (74.6)	30 (56.6)	0.065
iNO in first 48 hours	33 (62.2)	15 (28.3)	< 0.001
Cardiac Dysfunction, n (%)			
Any cardiac dysfunction	19 (37.3)	33 (62.3)	0.018
iNO in first 48 hours	18 (94.7)	12 (36.3)	< 0.001
ECMO utilization	13 (68.4)	12 (36.3)	0.043
Survival with cardiac dysfunction	9 (47.4)	27 (81.8)	0.014
Type of dysfunction (among those with dysfunction), n (%)			
RV dysfunction	8 (42.1)	16 (48.4)	0.775
LV dysfunction	4 (21.1)	2 (6.1)	0.175
RV + LV dysfunction	7 (36.8)	15 (45.5)	0.575
Vasoactive and vasodilator use, n (%)			
Dopamine	33 (64.7)	1 (1.9)	< 0.001
Epinephrine	6 (11.8)	31 (58.5)	< 0.001
Calcium gluconate	2 (3.9)	25 (47.2)	< 0.001
Abbreviations: ECMO = extracorporeal membrane oxygenation, SD = standard deviation, HFOV = high-frequency oscillatory ventilation, iNO = inhaled nitric oxide, RV = right ventricular, LV = left ventricular, PGE1 = prostaglandin E1			

Variable	Historical Cohort (n = 51)	Post-Guideline Cohort (n = 53)	p-value
Primary outcomes			
Norepinephrine	14 (27.5)	30 (56.6)	0.0031
Milrinone	20 (39.2)	19 (35.9)	0.840
PGE1	2 (3.9)	23 (43.4)	< 0.001
Sildenafil	27 (52.9)	23 (43.4)	0.433
Treprostinil	0 (0)	8 (15.1)	0.006
Inhaled prostacyclin	7 (13.7)	5 (9.4)	0.551
Discharge respiratory support, n (%)			
Room air	29 (82.8)	37 (78.7)	0.781
Nasal cannula	4 (11.4)	6 (12.8)	1
Tracheostomy	2 (5.7)	4 (8.5)	1
Room air	29 (82.8)	37 (78.7)	0.781
Length of stay, days, median [IQR]	40.0 (28.0–94.0)	54.0 (30.0-130.0)	0.196
Abbreviations: ECMO = extracorporeal membrane oxygenation, SD = standard deviation, HFOV = high-frequency oscillatory ventilation, iNO = inhaled nitric oxide, RV = right ventricular, LV = left ventricular, PGE1 = prostaglandin E1			

2. Survival, ECMO Utilization and Cardiac Dysfunction

Our primary outcome of overall survival to hospital discharge was significantly higher in the post-guideline cohort (68.6% vs. 88.7%, $p = 0.016$) (Fig. 2A). In the post-guideline cohort, ECMO utilization decreased from 51.0% to 26.4% ($p = 0.015$) and ECMO survival trended higher (42.3% vs. 71.4%, $p = 0.104$) (Fig. 2A). Importantly, analysis of outcomes stratified by CDH severity based on prenatal parameters revealed an improvement in survival and decreased ECMO utilization for each severity cohort in the post-guideline cohort (Fig. 2C).

The initial postnatal echo was performed at a median time of 2 hours in the post-guideline cohort compared to a median time of 4 hours in the historical cohort ($p = < 0.001$). With greater emphasis on the identification of cardiac dysfunction and post-repair monitoring of pulmonary hypertension, the post-guideline cohort received a greater total number of echocardiograms during their NICU stay (3 vs 7, $p = < 0.001$) (Table 2). Cardiac dysfunction was identified in the first 24 hours in a higher proportion of the post-guideline infants with CDH (37.3% vs 62.3%, $p = 0.02$) (Fig. 2B), which may reflect increased

surveillance of cardiac dysfunction as opposed to a true increase between the two cohorts. In the post-guideline cohort RV dysfunction was most common in 16 (30.2%) infants followed by RV + LV dysfunction in 15 (28.3%) infants and only 2 (3.7%) infants had isolated LV dysfunction.

We next interrogated rates of survival and ECMO utilization among infants with CDH with isolated RV or LV dysfunction or RV + LV dysfunction. In the post-guideline cohort, we observed 100% survival in infants with isolated RV or LV dysfunction (Fig. 3A). Infants with combined RV + LV dysfunction trended towards improved survival in the post-guideline cohort, though this did not meet statistical significance (28.5% vs 60.0%, $p = 0.362$). Overall, ECMO utilization decreased for infants with cardiac dysfunction in the post-guideline cohort (68.4% vs 36.3%, $p = 0.043$) (Fig. 2B).

We characterized the change in cardiac function over time in the post-guideline cohort (Fig. 3B). 86.8% of infants in the cohort had normal cardiac function at 72 hours of life and all infants with isolated LV and all but one with RV dysfunction had resolution. There remained a component of dysfunction in 6 infants with RV + LV dysfunction, and all 6 of those infants required ECMO.

3. Change in vasoactive and pulmonary vasodilator use

The physiology-driven guideline strongly recommended against dopamine use with its unfavorable effect on pulmonary vascular resistance^{17,35} and to limit iNO use in the setting of LV or RV + LV dysfunction, so we next characterize differences in the use of vasoactive medications and pulmonary vasodilators among the two cohorts (Figs. 3C-D). Dopamine use decreased from 64.7% to 1.9% ($p < 0.001$) whereas low-dose epinephrine administration increased from 11.8% to 58.5% ($p < 0.001$) in the historical cohort compared to the post-guideline cohort, respectively. Norepinephrine use increased from 27.5% to 56.6% ($p = 0.0031$) and calcium gluconate infusions increased from 3.9% to 47.2% ($p < 0.001$). There was no significant change in milrinone use.

There were also no changes in sildenafil or inhaled prostacyclin use between the two cohorts. No infants received IV treprostinil in the historical cohort, compared with eight infants in the post-guideline cohort ($p = 0.006$). This reflected a shift in practice with treprostinil being added as a pulmonary vasodilator in the post-guideline cohort, but not for the historical cohort. Inhaled nitric oxide use during the hospital stay showed a decreased trend from 74.6% to 56.6% ($p = 0.065$) with a significant decrease in iNO use during the first 48 hours of life from 62.2% to 28.3% ($p < 0.001$) in the post-guideline cohort. In infants with cardiac dysfunction, iNO use in the first 48 hours dropped significantly from 94.7% to 36.3% ($p < 0.001$) of infants. PGE1 therapy increased in the post-guideline cohort from 3.9% to 43.4% ($p < 0.001$). Together, these data support recognition and treatment of cardiac dysfunction with targeted vasoactive therapy as part of comprehensive care guidelines to optimize outcomes in infants with CDH.

Discussion

This is the largest single-center cohort study reporting early identification and treatment of cardiac dysfunction in infants with CDH. Early identification of cardiac dysfunction, implementation of a core multidisciplinary CDH team, and physiology-driven resuscitation and care guidelines resulted in an increase in survival and decrease in ECMO requirement overall and in infants with cardiac dysfunction in our single center.

Center variation in outcomes is not unique to CDH and is widely reported for many neonatal specific diseases such as the incidence of bronchopulmonary dysplasia (BPD) ^{36, 37, 38}, very low birth weight (VLBW) infants ^{39, 40, 41}, gastroschisis ⁴², and congenital heart disease ⁴³. Prior reports have suggested high volume (> 7–10 cases per year) CDH centers have improved mortality ^{23, 24, 44} and lower recurrence rates ⁴⁵. There also exist individual high performing centers ^{13, 14, 46, 47} whose reported outcomes are better than national datasets. This association between higher volumes of infants with CDH and improved outcomes suggests that increased exposure and expertise in complex cardiorespiratory physiology is a modifiable factor in improving outcomes. While center volume remained consistent at a median of 9 CDH infants a year, we improved expertise and exposure via creation of a focused CDH care team and geographic cohorting of infants. This approach has been described for other NICU-specific diagnoses with the creation of BPD-specific teams ³⁷ and teams dedicated to the care of VLBW infants ^{48, 49}. With this consistent care team, we have seen our primary outcome of survival to discharge improve to 88.7% and ECMO utilization decrease to 26.4%. The existence of a dedicated team, however, does not guarantee improved outcomes. The care delivered must be consistently guided by physiology coupled with current literature and a quality improvement mentality to bridge remaining gaps in evidence ⁴⁷. We hypothesized that early recognition and treatment of cardiac dysfunction is another modifiable factor to improve outcomes in infants with CDH based on several reports which identify ventricular function as a determinant in outcomes ^{6, 7, 8, 21, 22, 50}. Increasing recognition of cardiac dysfunction and its interplay with pulmonary hypertension have led to the identification of specific phenotypes that can guide targeted therapy for infants with CDH ^{2, 9}. These phenotypes, while imperfect, allow for identification of a mild phenotype, an RV phenotype with pulmonary hypertension and RV dysfunction, and a LV or RV + LV dysfunction phenotype with post-capillary pulmonary hypertension. We describe performing an early echocardiogram so that subsequent therapy can target the specific phenotype present (Fig. 1B). We did not see any physiologic disturbance or intolerance during the early postnatal echo in infants with CDH. We found that two-thirds of the post-guideline cohort had some form of cardiac dysfunction. Our results mirror that of Patel et al with RV and RV + LV dysfunction being more common than isolated LV dysfunction ⁹. No infants with normal cardiac function on the first postnatal echo developed dysfunction later in their course, and cardiac function was normal by 72 hours in 86.8% of the cohort (Fig. 3B). The 6 infants with RV + LV dysfunction that did not normalize ultimately required ECMO support. This is consistent with, and reinforces, data demonstrating that infants with biventricular dysfunction are at the greatest risk for morbidity and mortality ^{8, 9, 22}. Early identification of RV + LV dysfunction may allow for targeted treatment to improve outcomes in this cohort and provides additional data for use in the decision around need for ECMO support.

In addition, the new approach couples the treatment of cardiac dysfunction with guidelines to decrease inhaled nitric oxide (iNO) use in the setting of LV or RV + LV dysfunction and to discontinue the use of dopamine^{17, 35, 51}. The historical approach to blood pressure management in the NICU was to utilize dopamine as a first line vasoactive after fluid administration. However, dopamine has a dose-dependent receptor selectivity resulting in variable physiologic effects and has an unfavorable action on PVR^{17, 35}. Instead, we implemented a more targeted vasoactive approach to complex CDH physiology. If cardiac dysfunction was identified, we intervened with low-dose epinephrine and calcium gluconate infusions. We sought to balance the treatment of cardiac dysfunction and pulmonary hypertension by utilizing a ventilator strategy that prevents hyperinflation, and subsequent elevations in PVR, and decreases in lung compliance. This was coupled with maintenance of ductal patency with PGE1 in infants with systemic or suprasystemic pulmonary hypertension^{28, 29}. Our data show that dopamine use was discontinued, targeted treatment of cardiac dysfunction was common, and that PGE1 use increased significantly in the post-guideline cohort. A complete approach to infants with CDH is necessary for success. It is not just identification of cardiac dysfunction, but a treatment strategy that focuses on concomitant pulmonary hypoplasia and pulmonary hypertension.

While this is the largest single center CDH cohort reporting early identification and treatment of cardiac dysfunction, it remains limited by the single-center nature. We do not use targeted neonatal echocardiography (TNE) at our center, therefore while LV function is objective, there remains subjectivity in the identification of RV dysfunction. There was a great deal of heterogeneity in the care of infants with CDH in the historical cohort, so we cannot say with certainty which intervention has resulted in improved outcomes. However, it is clear from this data that cardiac dysfunction is prevalent and can complicate the transition to extra-uterine life in infants with CDH. The strength of this study is that we leverage a NICU team approach with existing pediatric cardiology resources to identify cardiac dysfunction. This approach does not require additional training in TNE or neonatal hemodynamics and is a generalizable approach for centers that do not have a neonatal hemodynamics program.

These data add to the growing body of literature that recognition and intervention of cardiac dysfunction is equally as important as the care of pulmonary hypoplasia and pulmonary hypertension. We present our approach to the management of cardiac dysfunction, but we do not want to overshadow the role gentle ventilation, targeted use of pulmonary vasodilators, excellent surgical partnership, nutrition⁵², and high fidelity ECMO⁵³ play in the outcomes of infants with CDH. The ability of a multi-disciplinary team to work together to deliver high fidelity intensive care is key to improving outcomes in this population.

Conclusion

A dedicated care team improves expertise and consistency in the care of infants with CDH and cardiac dysfunction is prevalent in early postnatal echocardiograms of infants with CDH. A targeted postnatal echo is well tolerated and often yields clinically relevant information. We report a generalizable approach to identification and treatment of cardiac dysfunction that improved outcomes in our single-center

cohort. Infants with RV + LV dysfunction have the highest ECMO utilization and highest mortality in our cohort. This phenotype remains the most refractory cohort to treatment, suggesting additional study and development of specific care strategies to decrease ECMO utilization and improve survival are needed.

Declarations

Conflict of Interest: All authors declare no competing financial interests.

Ethics and Consent to Participate: This study was approved by the Washington University in St. Louis Institutional Review Board (#202510238)

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Author Contributions:

Patrick E. Sloan: data collection, designed the study, statistical analysis, and drafting of the manuscript.

Lila S. Sanning: review, statistical analysis and drafting of the manuscript

Caren Liviskie: review and statistical analysis of the manuscript

Kristen Clark: review of the manuscript

Kylie Bushroe: review of the manuscript

Melissa Riley: review of the manuscript

Anna Lijowksa: review of the manuscript

Jesse Vrecenak: designed the study and review of the manuscript

Tasnim Najaf: designed the study, statistical analysis, and drafting of the manuscript.

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Figures

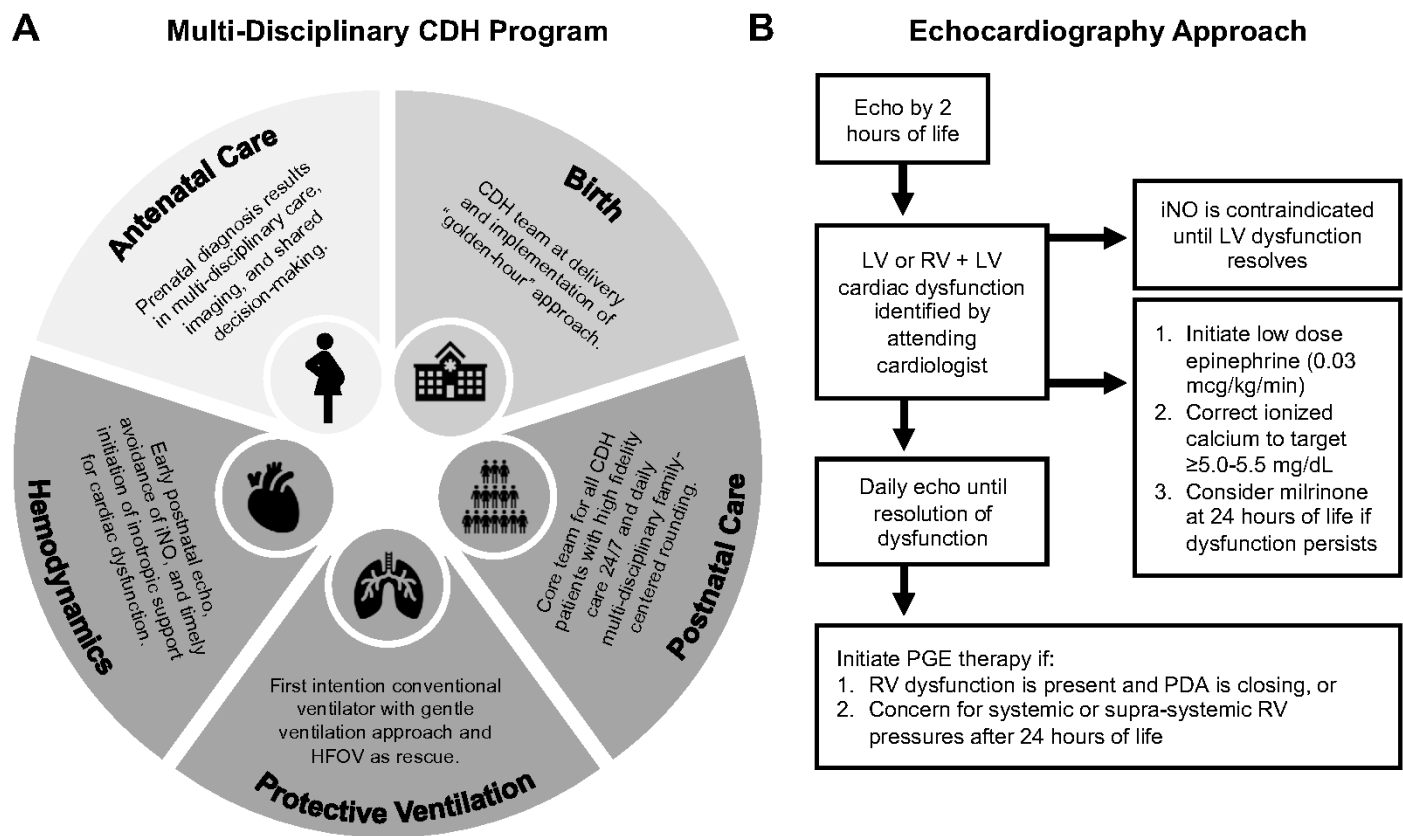


Figure 1

A multi-disciplinary care team and early recognition of cardiac dysfunction support improved care of CDH infants. **A.** A comprehensive and multi-disciplinary approach to the care of CDH infants spans from antenatal counseling, a dedicated delivery team, and guideline-based postnatal management. **B.** Echocardiographic algorithm for the diagnosis and intervention of cardiac dysfunction in CDH. *Abbreviations: HFOV: high frequency oscillatory ventilation, iNO: inhaled nitric oxide, LV: left ventricular, PDA: patent ductus arteriosus, PGE: prostaglandin E1, RV: right ventricular.*

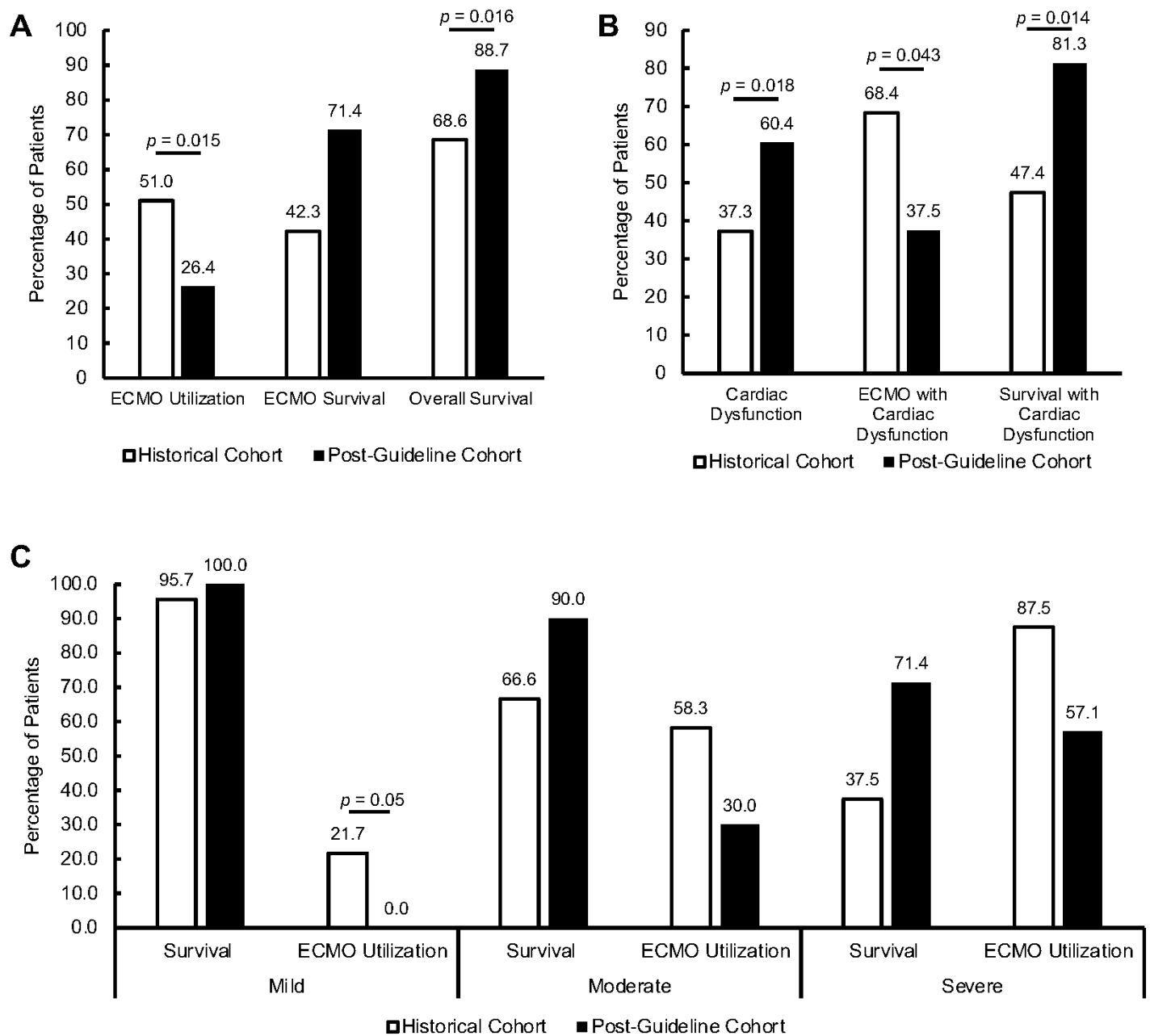


Figure 2

Survival to discharge, ECMO survival and ECMO utilization. **A.** Comparison of primary outcomes in the historical and post-guideline cohort. **B.** Comparison of rates of cardiac dysfunction and outcomes for patients with cardiac dysfunction between the historical and post-guideline cohort. **C.** Comparison of survival and ECMO utilization in the two cohorts of infants with mild, moderate, or severe CDH.

Abbreviation: ECMO: extracorporeal membrane oxygenation.

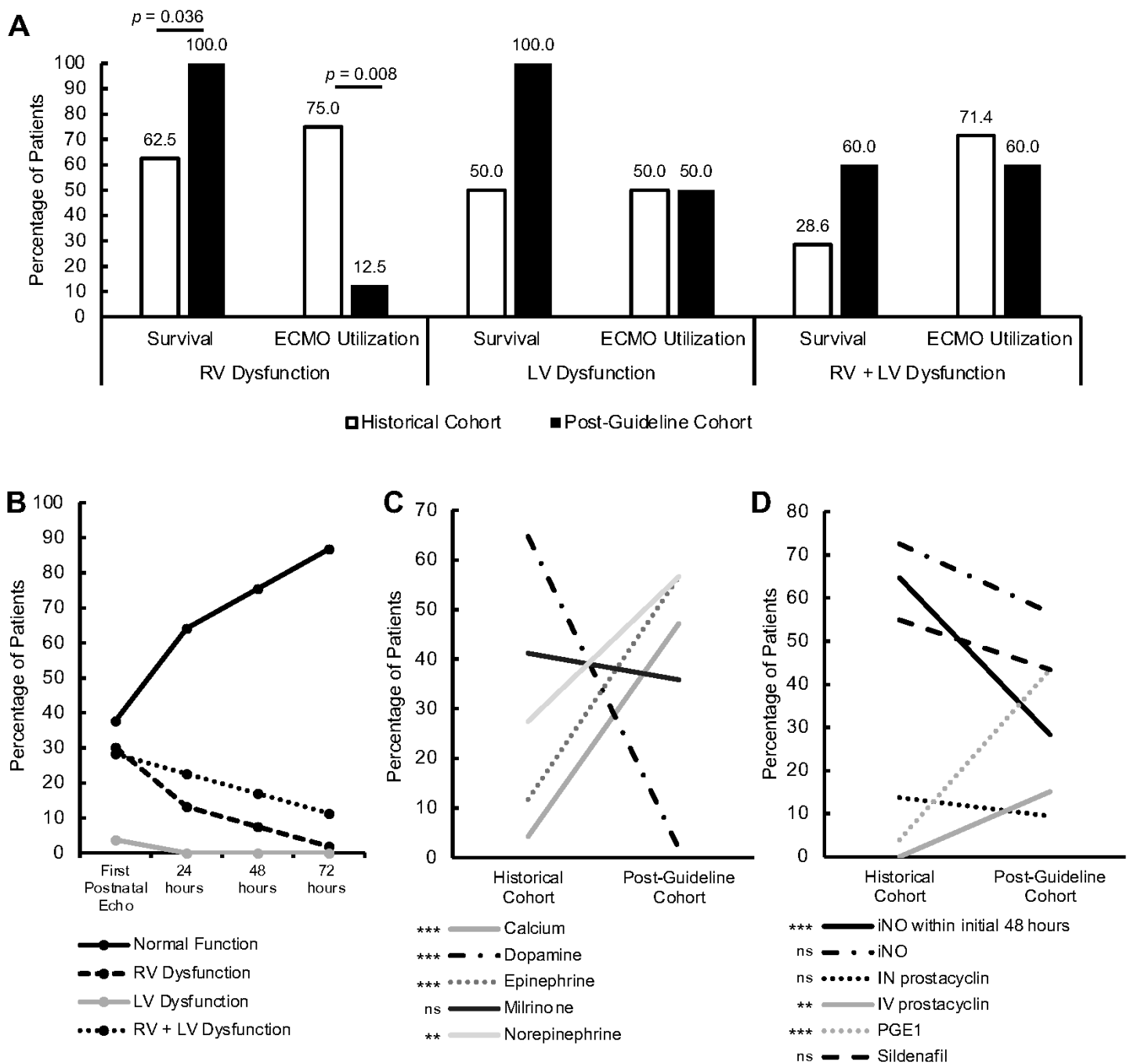


Figure 3

Outcomes stratified by type of cardiac dysfunction and changes in vasoactive use with guideline implementation

A. Comparison of survival and ECMO utilization in the historical and post-guideline cohorts of infants with CDH with either RV, LV, or RV+LV dysfunction. **B.** Changes in cardiac function over the first 72 hours in the post-guideline cohort. **C-D.** Changes in vasoactive and vasodilator use between the two cohorts. *** $p < 0.001$, ** $p < 0.01$, ns: not significant

Abbreviations: ECMO: Extracorporeal membrane oxygenation, iNO: inhaled nitric oxide, IN: inhaled, IV: intravenous, LV: left ventricular, PGE1: prostaglandin E1, RV: right ventricular.

