CDH Treatment and Outcomes: What we've learned.

David W. Kays, MD
Director Center for Congenital Diaphragmatic Hernia
Director Extracorporeal Life Support
Johns Hopkins All Children's Hospital

JOHNS HOPKINS
All Children's Hospital

Background

- Trained in Pediatric Surgery at Columbia University
  - Credit Charlie Stolar
  - Credit Jen Wung
  - Credit Jay Wilson
  - Credit Kevin Lally
  - Thank Matt Harting and the CDH community for asking me to speak

I have no disclosures

- >450 CDH patients

- 321 at University of Florida
  - 1992 - 2015

- > 140 patients at Johns Hopkins All Children's Hospital
  2016 - present

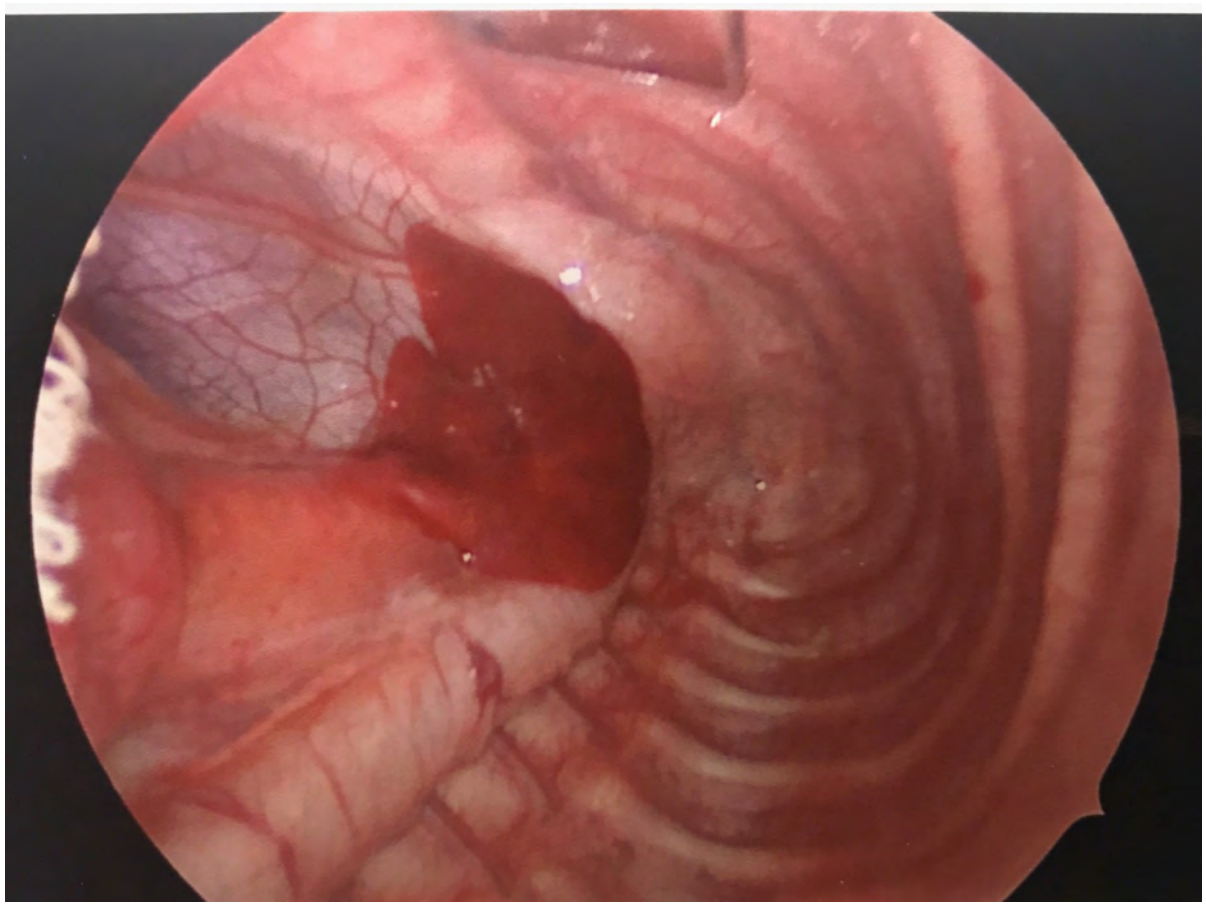
Outline

- Describe our population
  - 101 consecutive CDH cases at JHACH
  - Describe them by risk stratifiers
    - Anatomy, lung volumes, physiology, associated anomalies
- Describe the care paradigm
  - Foundational principles
  - Ventilation
  - **Focus on ECMO**
  - **Focus on Repair**

Describe Outcomes

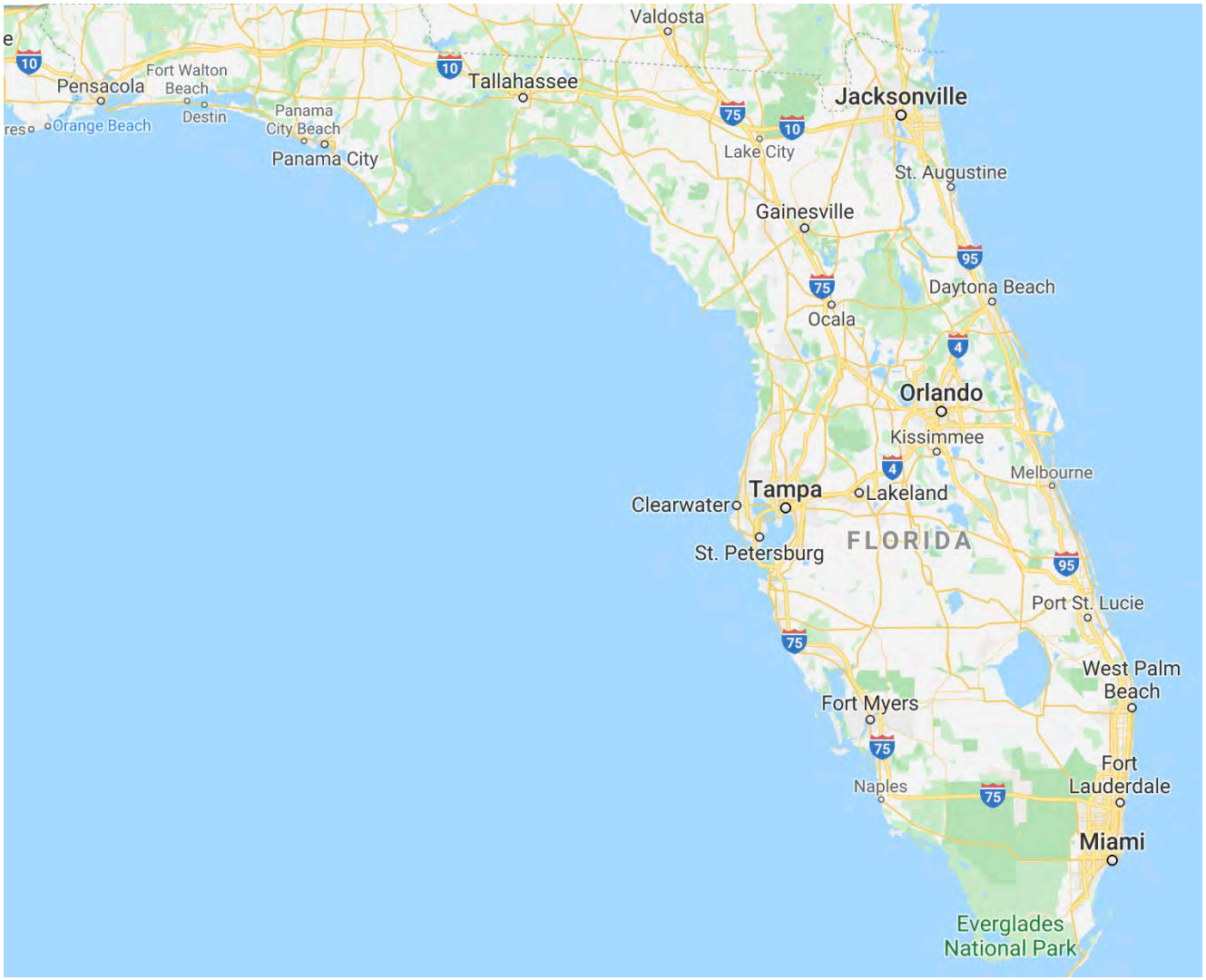
- Survival
- Time in hospital
- Outcomes
  - Neuro imaging outcomes (gross)
- Conclusions

This is the disease: Pulmonary Hypoplasia (highly severe)



CDH Referral Pattern

High volume Referral Center
High percentage of prenatally diagnosed and evaluated patients
Increased Severity


Valdosta
Pensacola
Fort Walton Beach
Destin
Orange Beach
Panama City Beach
Panama City
Tallahassee
Jacksonville
Lake City
St. Augustine
Gainesville
Daytona Beach
Ocala
Orlando
Kissimmee
Melbourne
Tampa
Lakeland
Clearwater
St. Petersburg
FLORIDA
Port St. Lucie
West Palm Beach
Fort Myers
Naples
Fort Lauderdale
Miami
Everglades National Park

Johns Hopkins All Children's St Petersburg, FL

Lessons Learned, treatments refined

- >450 CDH patients
- 321 at University of Florida
  - 1992 - 2015
- > 140 patients at Johns Hopkins All Children's Hospital
  2016 - present

Analogy: Golf

- Golf is a HARD game
- To succeed: ALL ASPECTS of your game need to be good
  - Drives
  - Long irons
  - Short irons
  - Chipping
  - Putting
  - Rescue

  - One bad shot can ruin any hole

CDH care is hard.

To succeed at CDH care, it's not just one thing.
There is no single "secret"

5 major lessons learned

- **-Lungs: the primary key to survival**
- **-Repair: the second key to survival**
- **-ECMO: Critical to save the worst**
  - **-Must do Better ECMO**
- **-Risk stratification: know your patient**
- **-Offer your best therapy to your sickest patients**
- **-Belief: they do have enough lung to survive**

Detrimental Effects of Standard Medical Therapy in Congenital Diaphragmatic Hernia

David W. Kays, MD, Max R. Langham, Jr., MD, Daniel J. Ledbetter, MD, and James L. Talbert, MD

From the Department of Surgery, Division of Pediatric Surgery, University of Florida, and The Shands Children's Hospital at the University of Florida, Gainesville, Florida

Hypothesis:

- Hyperventilation/alkalosis is harmful to CDH patients
- Elimination of this therapy will result in improved survival
- Prospective change in therapy in August, 1992

Annals of Surgery. 1999. 230(3) 340-351
Kays, Langham, Ledbetter, and Talbert

CDH: Treatment Strategy

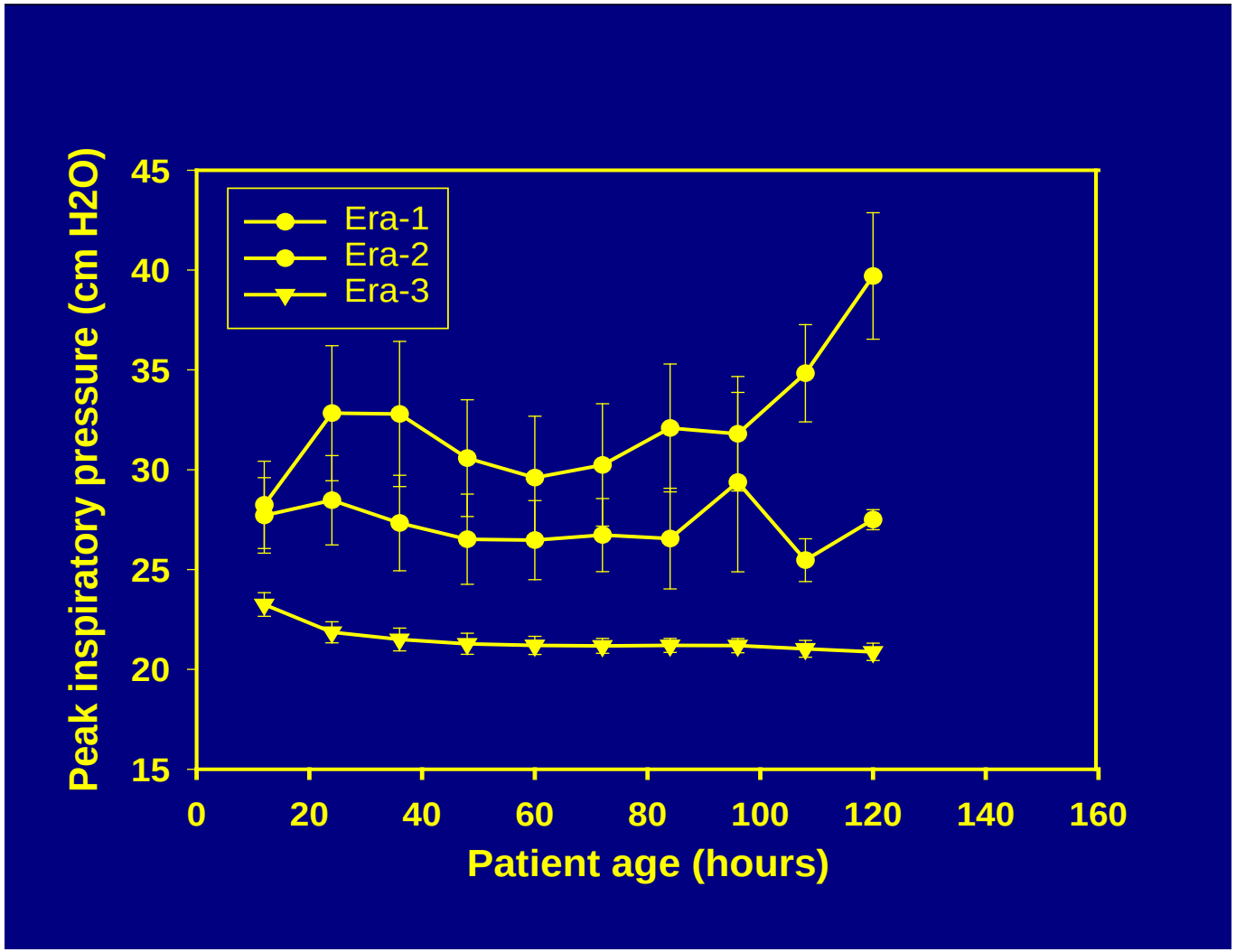
- Light to moderate sedation (no paralysis)
- Conventional SIMV pressure-limited ventilation with rate set to patient comfort and clinical state
- Lowest pressure which provides adequate chest movement (usually 20 - 24 cm H2O)
- Hyperventilation and alkalosis are strictly avoided

Annals of Surgery. 1999. 230(3) 340-351

Indications for ECMO

- Inability to maintain and insure adequate oxygen delivery to the brain
  - Pre-ductal sats < 85%
  - NIRS < 50%
  - Despite optimal support

Mean PIP over 120 hours



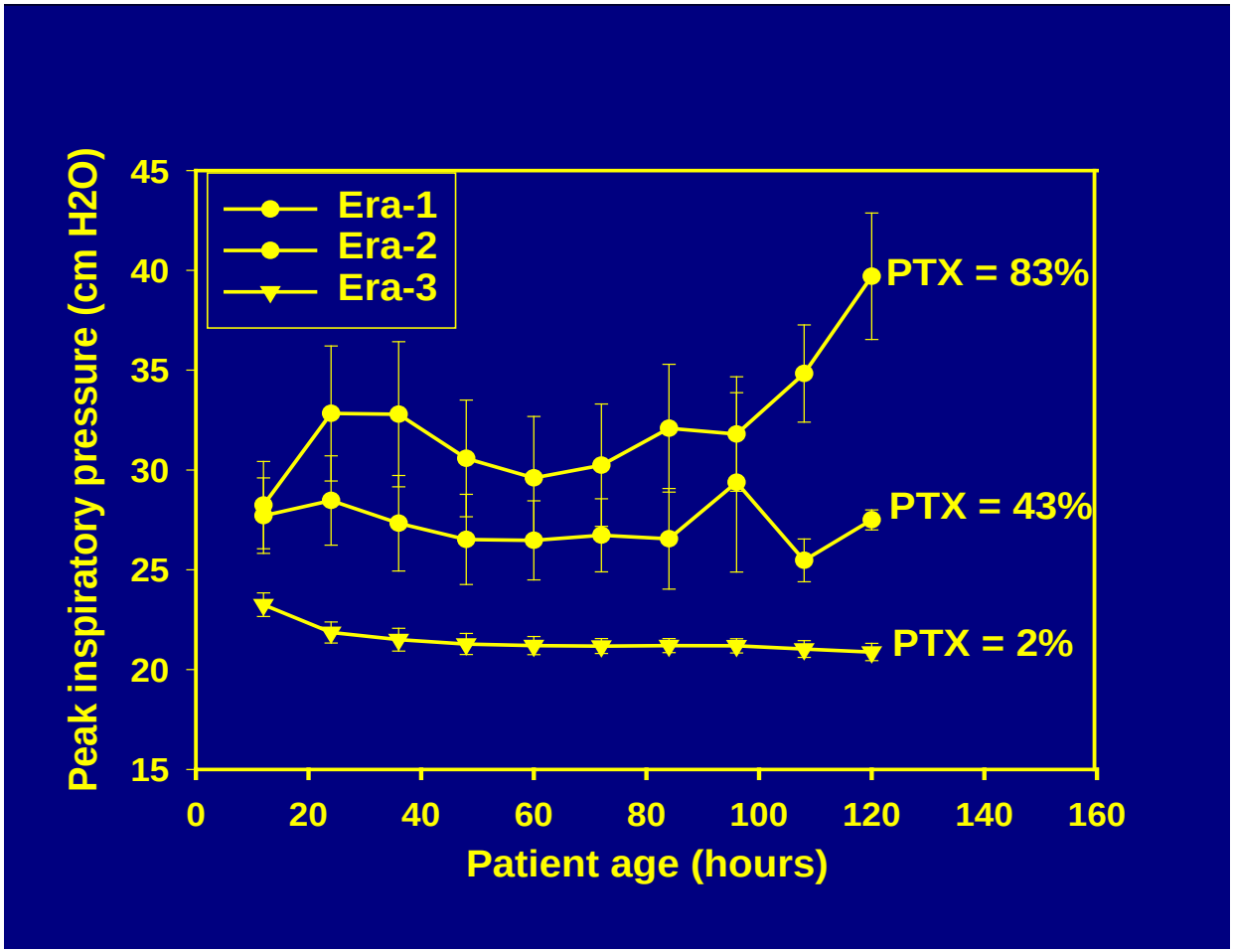
Mean +/- SEM

p<0.05 at all time points

p=0.00001

Time*Era effect

Mean PIP over 120 hours



Mean +/- SEM

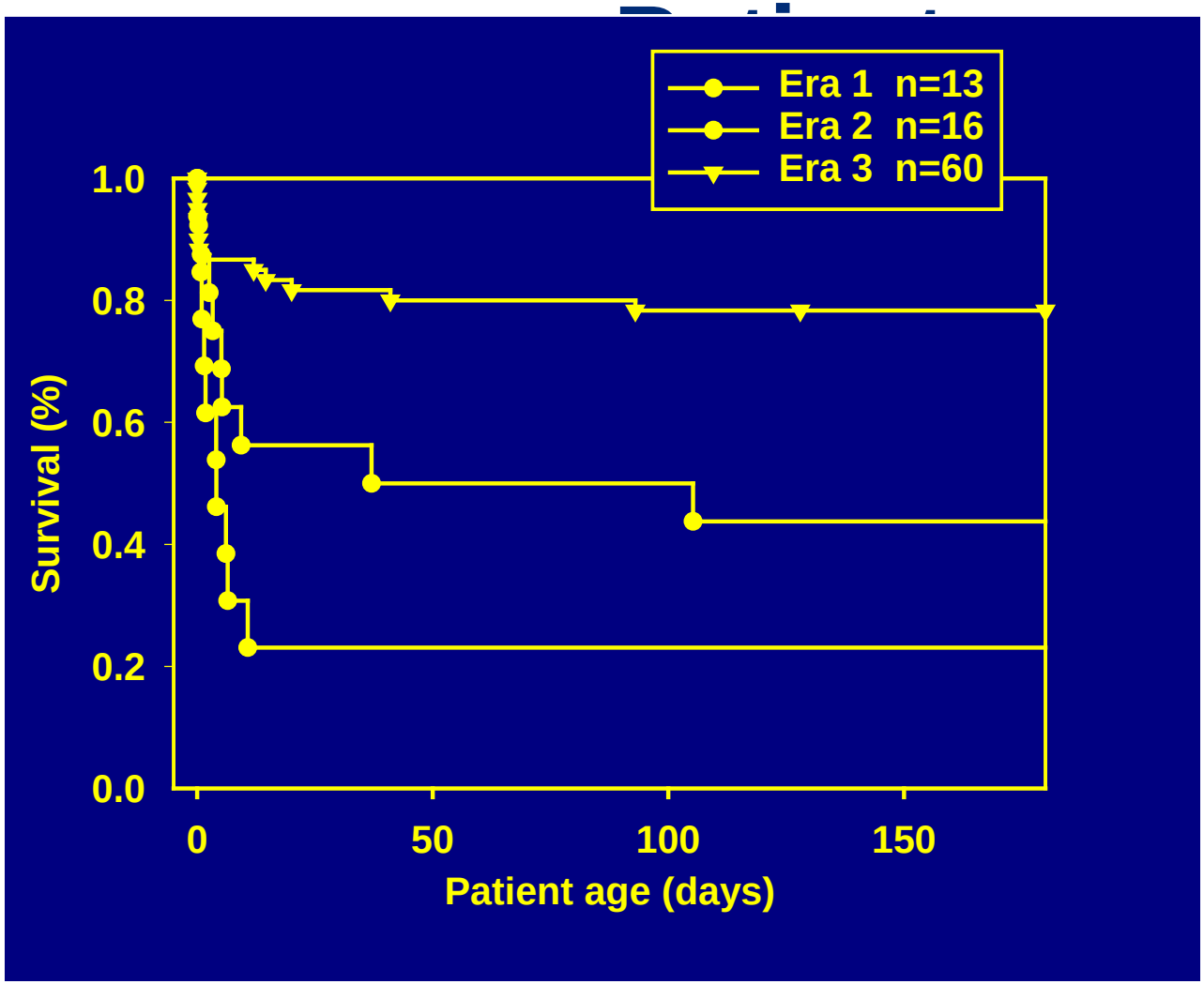
p<0.05 at all time points

p=0.00001

Time*Era effect

Annals of Surgery. 1999. 230(3) 340-351

Survival Curve by Era, All Patients



Survival Graph
p<0.0001

Annals of Surgery. 1999. 230(3) 340-351

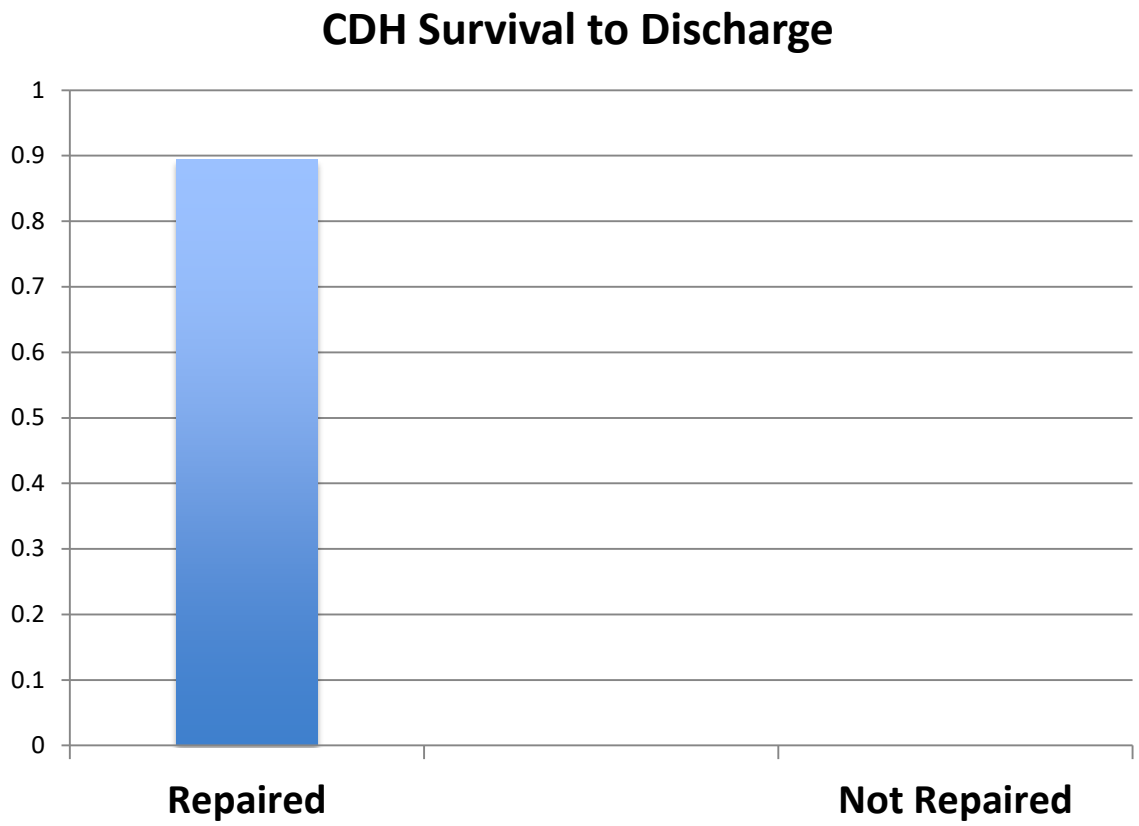
CDH Treatment Fundamental #1

Must eliminate any iatrogenic lung injury:

The number of CDH patients that survive is all about how well we take care of their lungs

CDH Treatment Fundamental #2

- (2) Repair the Hernia (CDH) (n=268)



UF Data: Unpublished

When to repair

- Avoided ECMO:
  - Follow clinical course. When improvement plateaus, repair
  - Day 4 – 7 (mean 118 (+/- 27) hrs

Early repair before ECMO vs Delay and arrive to ECMO unrepaired (w/ opportunity)

	ECMO 1st n=20	Repair first n=22	P= (Mann-Whit)
Survived	**13 (65%)**	**21 (96%)**	**0.018**
Apgar-5	5.9	6.0	.610
CDH SG Surv	52.4	58.2	.364
1st LHR	1.1	1.1	.791
LHR o/e	30.6	28.5	.868
pH-1	7.1	7.1	.319
PO2-1	46.1	46.9	.705
PCO2-1	85.8	77.1	.307
Surv Eq 1	**.79**	**.77**	**.537**
ECMO risk-1	**.81**	**.83**	**.811**
ECMO risk-2	**.77**	**.80**	**.734**
Pred Surv w/o ECMO	**.20**	**.16**	**.801**

Pros and Cons of "Repair before ECMO"

- Pros
  - It works. ECMO runs are easier, cleaner, better.
  - Minimal risk of bleeding
  - New comfort going to ECMO.
  - **Everyone gets repaired.**

- Cons
  - Repair becomes time sensitive:
  - Still concern could increase risk of ECMO

  - BUT WHY ALL THIS EFFORT???

In early 2016, we transitioned from early repair “BEFORE ECMO”, to early repair ON ECMO

- Repair next am
- Ave time to ECMO: 30 hrs (+/- 33)
- Ave time to Repair: 65 hrs (+/- 69)
- Next morning is most common time for repair after initiating ECMO

Principle #3
Do Better ECMO

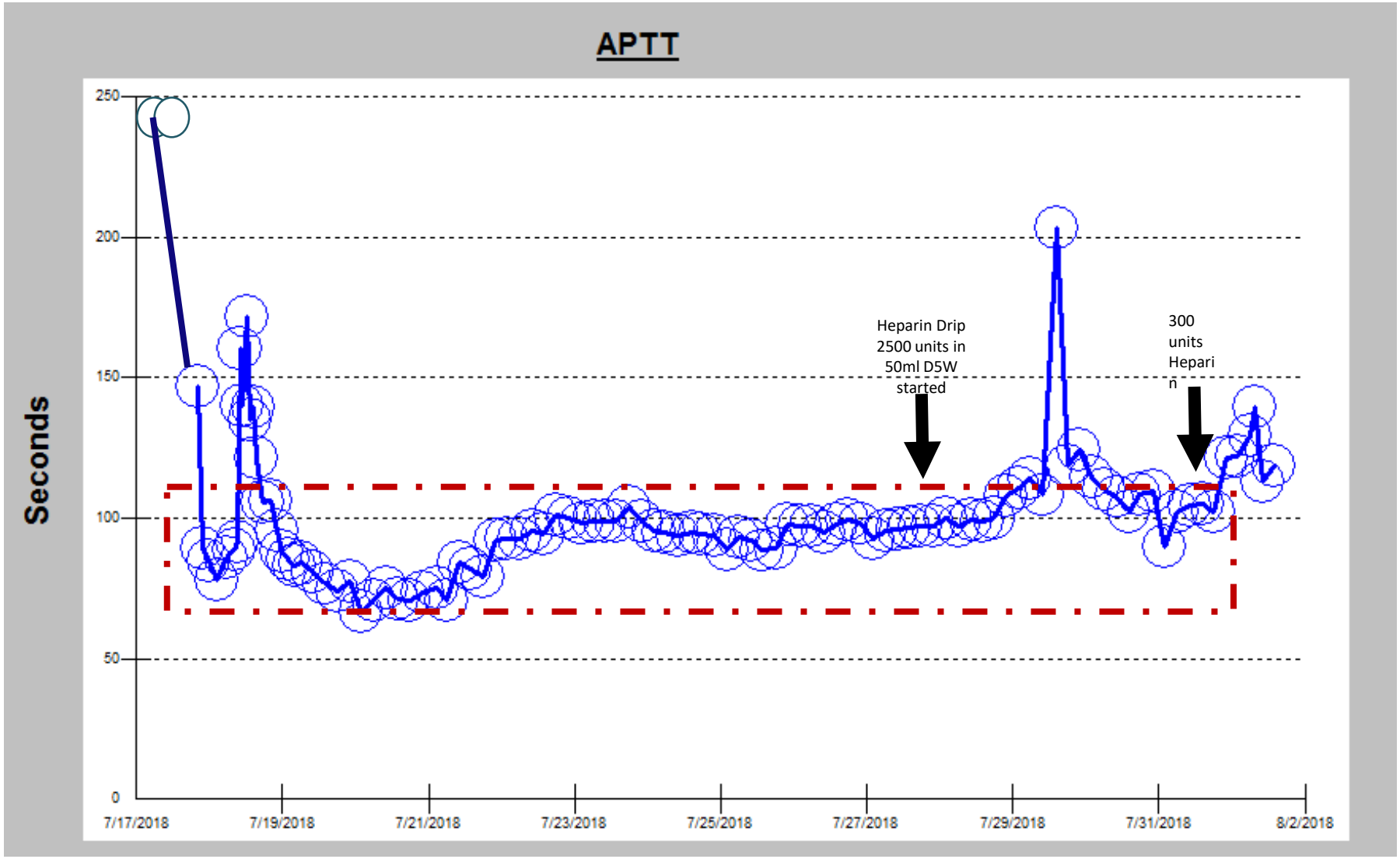
- Decision making and timing
- Better Circuits
- Better anticoagulation
- Better concepts
  - Support and weaning

Better ECMO:

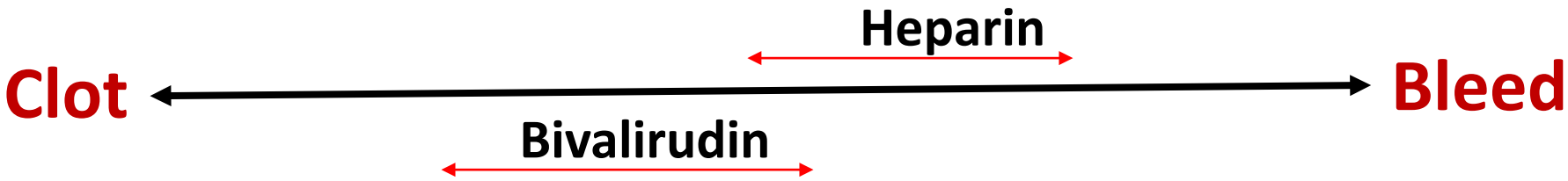
- All VA. (VV doesn’t unload RV nor PA’s)
- Repair early on ECMO. 24 hours
- Better anticoagulation:
  - Bivalirudin

Bivalirudin

- Direct thrombin inhibitor
- Clean
- Predictable
- Efficacy?
  - Bleeding vs clotting?
- Pharmacokinetics
  - 20% renal excretion
  - **80% proteolytic degredation**
    - ? Where ? (important)


APTT
Seconds
250
200
150
100
50
0
7/17/2018
7/19/2018
7/21/2018
7/23/2018
7/25/2018
7/27/2018
7/29/2018
7/31/2018
8/2/2018
Heparin Drip 2500 units in 50ml D5W started
300 units Heparin

Anticoagulant Properties (?)



ECMO Pumps

- Roller vs Centrifugal?
- Below 10 kg, not all centrifugal are created equal

Offer your best treatment to your sickest patients. Believe they can survive.

- What are the outcomes in ”the worst” CDH patients?
  - (Buckets A&B)

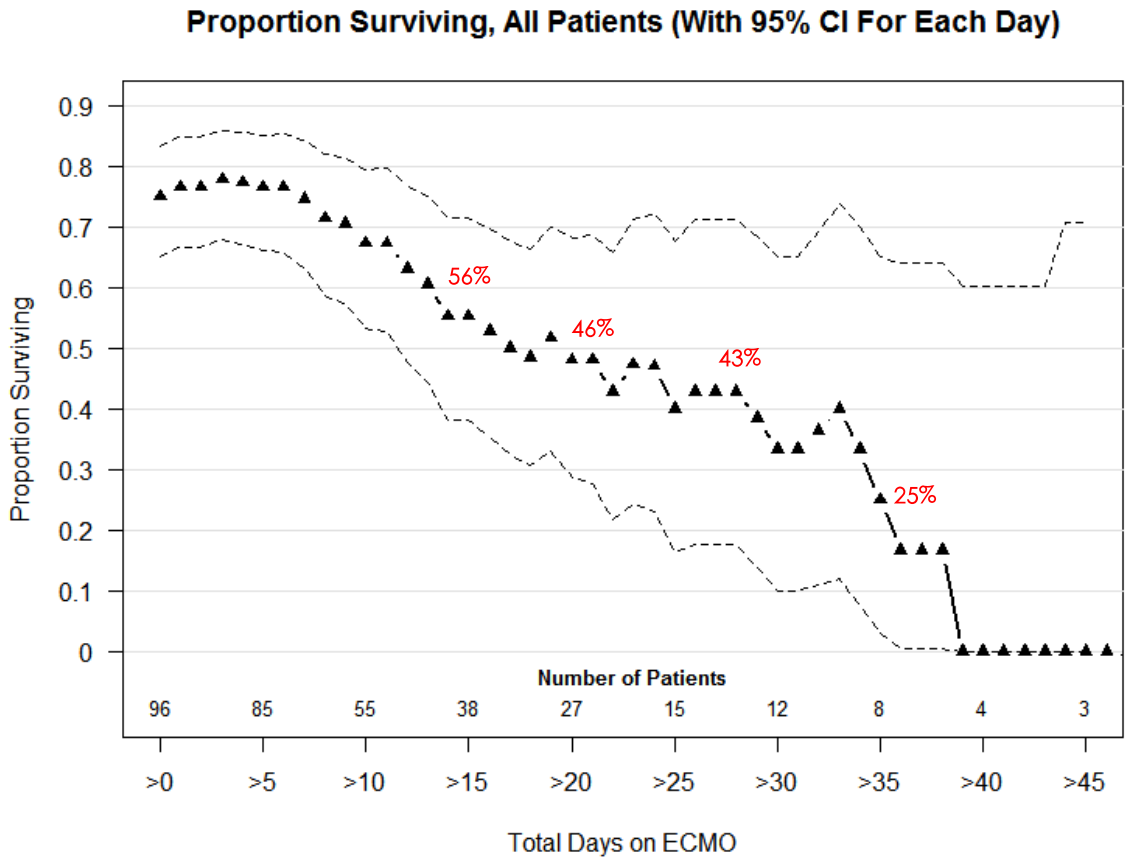
J Pediatr Surg. 2015 Jun;50(6):893-7
Kays DW, Islam S, Perkins JM, Larson SD, Taylor JA, Talbert JL

6.64 / >130 / 15

	GA	BW	Ap-1	Ap-5	Pred %	Side	pH-1	PCO2	PO2	ECMO	Surv	d/c-m	Resp d/c
1	28	1053	1	2	4	Left	6.59	> 100	16	No	No	*	*
2	39	2000	0	1	6	Left	6.75	> 100	41	Yes	Yes	3.2	100 cc NC
3	38	3200	1	2	23	Right	6.67	> 100	75	Yes	No	*	*
4	36	3939	1	2	38	Left	6.64	> 130	15	Yes	Yes	3.4	400 cc NC
5	35	2645	0	4	31	Left	6.75	106	59	Yes	No	*	*
6	37	2400	2	1	9	Left	6.76	> 100	41	Yes	Yes	2.9	100 cc NC
7	35	2040	1	4	21	Left	6.81	145	46	Yes	No	*	*
8	27	988	3	1	2	Left	6.8	> 100	8	No	No	*	*
9	37	2500	1	3	20	Left	6.88	> 100	33	Yes	Yes	3.7	300 cc NC
10	37	2212	1	3	16	Left	6.95	> 100	62	Yes	No	*	*
11	33	1250	3	4	11	Left	6.86	96	49	No	No	*	*
12	39	2450	1	1	9	Left	7.04	79	37	Yes	Yes	3.4	100 cc NC
13	34	2595	2	5	40	Left	6.85	> 130	37	Yes	No	*	*
14	35	1880	3	4	18	Left	6.93	> 100	21	Yes	Yes	3.6	100 cc NC
15	38	2750	1	2	17	Left	7.07	67	44	Yes	No	*	*
16	37	3590	0	4	52	Right	6.93	> 100	48	Yes	Yes	1.6	400 cc NC
17	38	3030	2	4	39	Right	6.88	> 100	33	Yes	Yes	4.2	100 cc NC

Most Severe 10%: (N=172) Survival 8/17 = 47%.

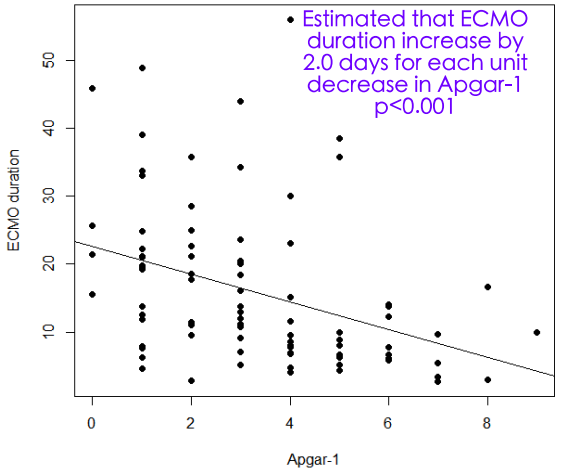
Survival vs Time on ECMO

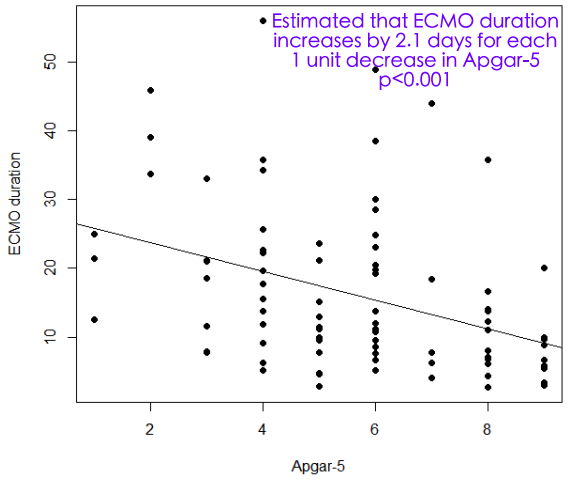


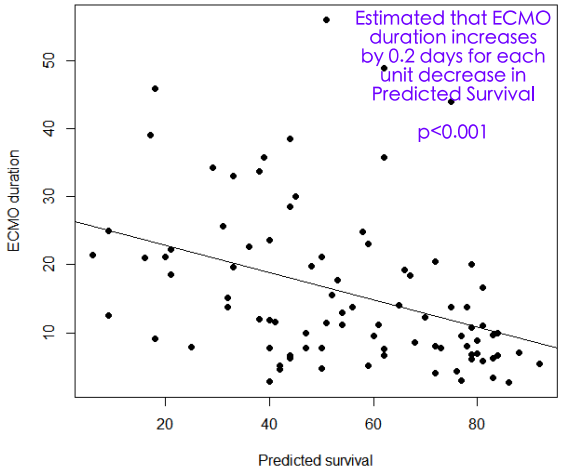
J American College of Surgeons, 2014

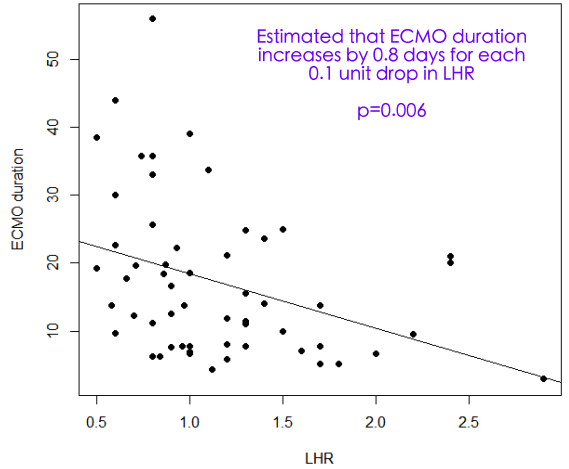
Kays, Islam, Larson, Perkins, Talbert

Association of risk factors with Duration



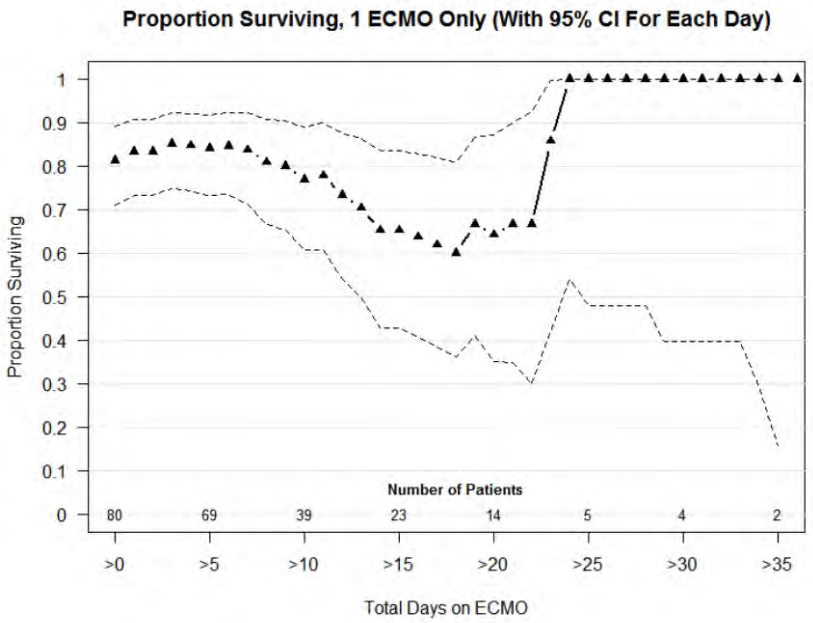




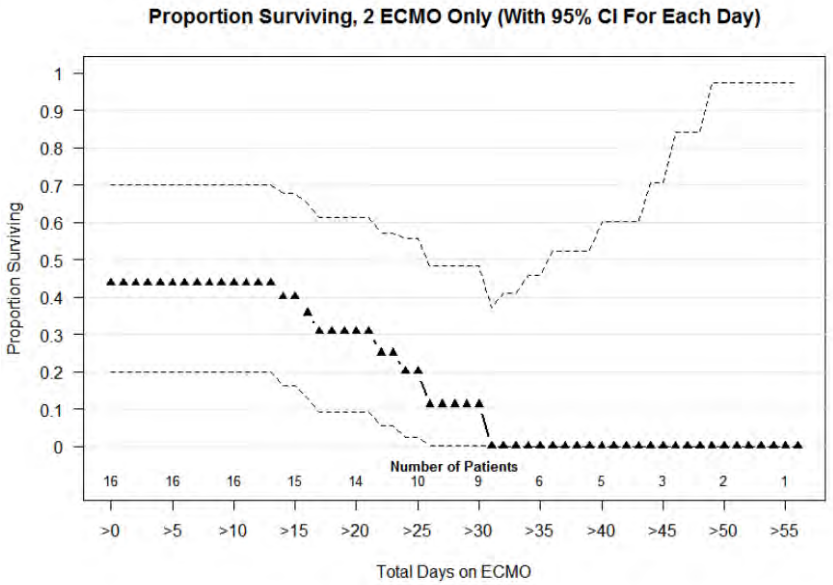


1St Run ECMO vs 2nd Run ECMO for CDH

1st Run ECMO



2nd Run ECMO



What if we put it all together?

- Protect lungs
- Risk Stratify Repair timing
- Get Everyone Repaired
- Do Great ECMO
  - Good decision making
  - Minimize errors
- Believe they can Survive
- What If ?

CDH Program @ JHACH

- 101 Consecutive patients
- Unselected. All-comers*
  - *2 patients seen at our program chose to deliver at their home hospital. Both FDIU
    - Bilateral CDH with 2% o/e TFLV
    - Trisomy 15 mosaic with hydrops

Our Paradigm

- CDH is about lung hypoplasia
  - All treatment decisions are about gas exchange and about helping little lungs work as well as they can.
  - Pulmonary Hypertension is a secondary issue, and does not drive management

Treatment Specifics

- Prenatally evaluation including
  - LHR, Echo, and MRI (o/e TFLV)
  - Counseling
- Inborn Delivery at 38 weeks or so
- Resuscitation in Delivery Room by CDH Team
  - CDH surgeon, CDH neonatologist, CDH RT, CDH nurses
  - (Roles meld and titles fade)
- Conventional ventilation,
  - PIP 25 or less
  - Pre-ductal sats most important
  - Nitric Oxide started for near ECMO level hypoxemia
    - Pre-ductal sats less than 85, PO2 less than 35
  - ECMO when unable to maintain pre-ductal sats at or near 80 - 85 despite optimization of support (brain protection)

Treatment Paradigm

- Risk stratify repair timing to minimize risk of ECMO
- Delay repair for 4 – 6 days (as long as improving)
- If goes to ECMO, repair within 24 hrs
  - Pediatric specific centrifugal or rollerhead pump
  - Bivalirudin probably better than heparin
  - Do GREAT ECMO: good decisions, good supportive care, time
  - Develop exceptional surgical technique and expertise
- Focus on lung function and gas exchange
  - Pulmonary hypertension is the symptom, not the disease
- Believe they can survive
  - Minimize Errors
  - Learn from mistakes
  - Simplify care

ECMO Management

- VA ECMO
- Pump:
  - Sorin Revolution at JHACH (3 patients then changed)
  - Pedi-Mag for all subsequent ECMO (14 cc prime)
- Anticoagulation
  - Changed to Bivalirudin (3/1/2016)

ECMO Weaning

- Athletic Training Paradigm
  - Wean ECMO at a (slow) rate that allows the heart and pulmonary vasculature to develop work capacity over time.
  - All ECMO patients started on sildenafil at 0.8 mg/kg/d when start wean phase (to help stabilize pulm vasc)
  - All patients successfully weaned and none required a second ECMO run.

Second Axis of Severity: CDH Groups (Buckets)

The full spectrum of CDH:

-Associated anomalies**: None**

-"**Isolated CDH**"

The full spectrum of CDH

-Associated anomalies**: less severe, not life threatening**

-ie. Small to moderate VSD, partial renal obstruction

-less severe genetic defects

The full spectrum of CDH

-Associated anomalies**: severe to life-threatening**

-**major chromosomal** (trisomy 13, 15, 18, others)

-**major heart defects. (STAT 3 or higher?)**

single ventricle physiology (HLHS, pulm atresia-VSD)

-bilateral CDH

-major abd wall defect: Giant Omphalocele

-major CNS anomaly

101 Consecutive patients

- Bucket A
- (Isolated)
- 71

- Full spectrum of disease

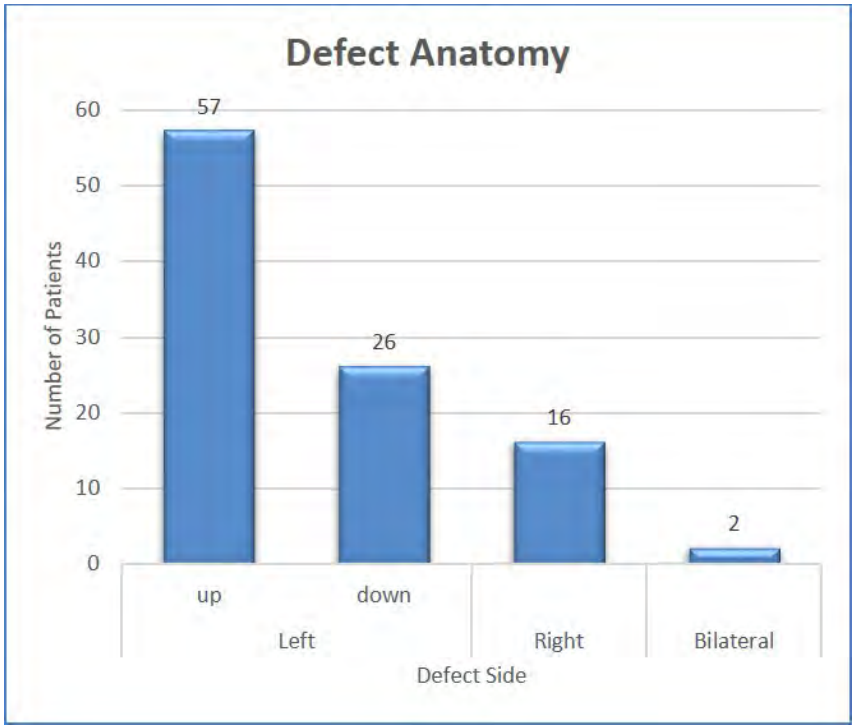
- Bucket B
- Assoc. Anomalies
- 20

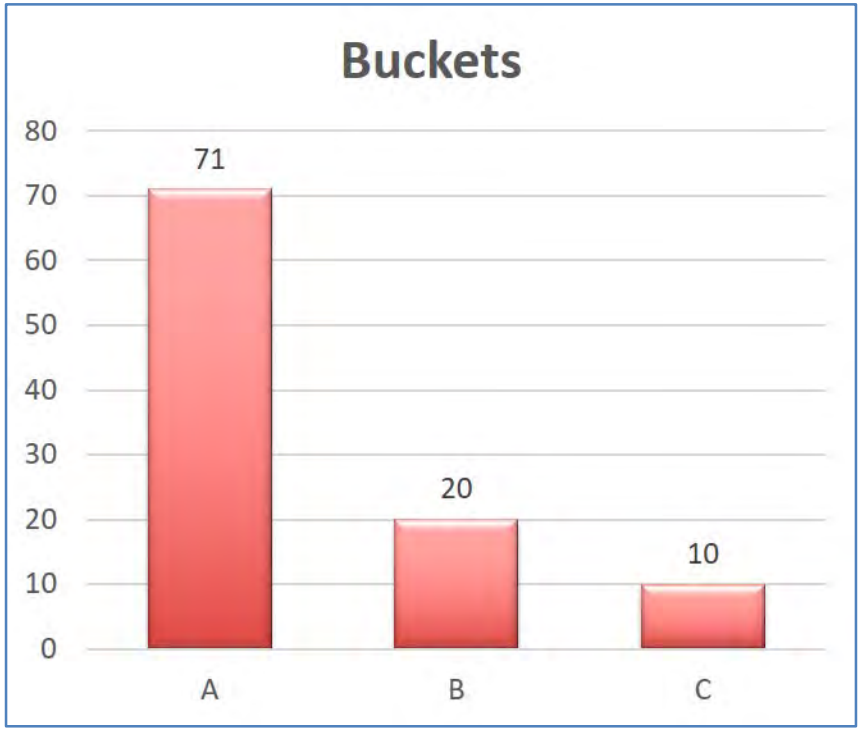
- Large VSD: 2
- DiGeorge Syndrome
- Neonatal Diabetes
- Kleinfelter
- Obstructive Uropathy
- Serious but non-lethal chromosomal abnormalities

- Bucket C
- Severe Assoc
- 10

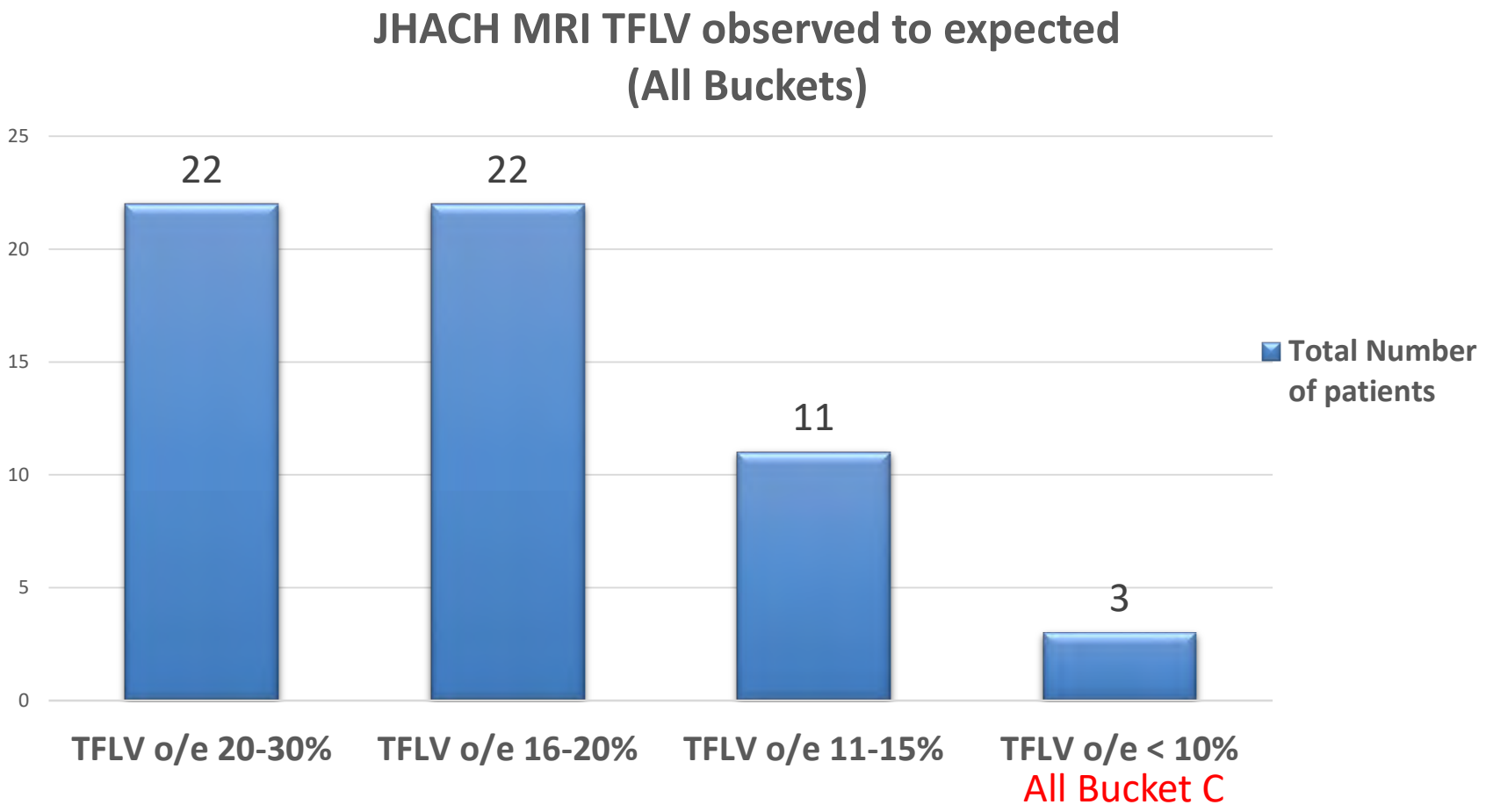
- Bilat CDH-2
  - TFLV 6% and 8%
- Complex Card-4
  - Single vent
  - Pulm atresia/VSD
  - TA w/ IAA
  - TAPVR w/ Em. Syn
- Giant Omph.-2
- Massive hydrocephalus

JHACH Patient Distribution





58 of 101 had TFLV o/e less than 30%. (58%)



9 worst patients by 1 hour ABG

Patient	pH @ 1 hour	PCO2 @ 1 hours	PO2 2 1 hour
1	**< 6.80**	**> 134**	50
2	**< 6.80**	**> 112**	46
3	**6.83**	**> 112**	64
4	**6.85**	**> 122**	29
5	**6.91**	**91**	43
6	**6.94**	**> 134**	32
7	**6.96**	**116**	31
8	**6.96**	**119**	51
9	**6.99**	**103**	49

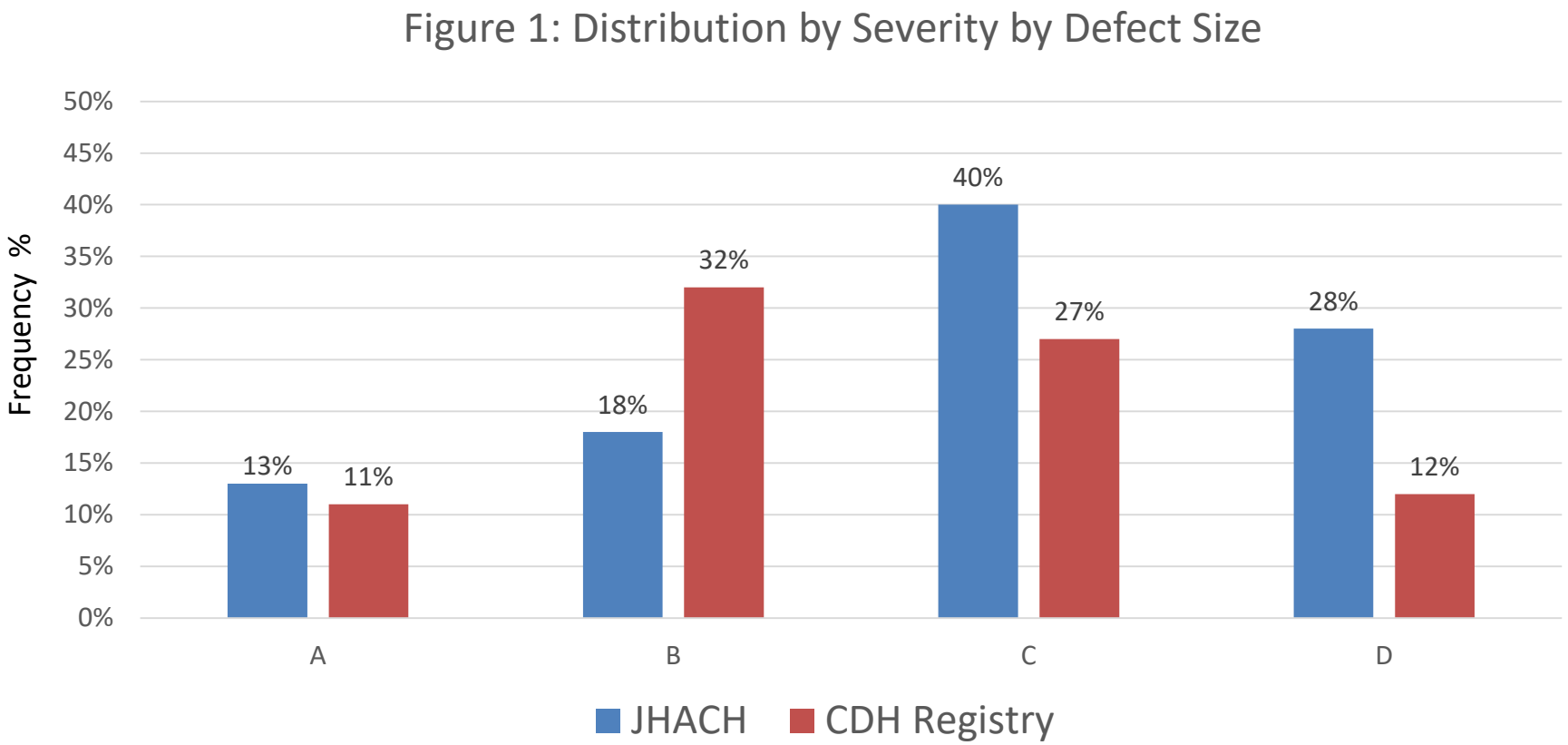


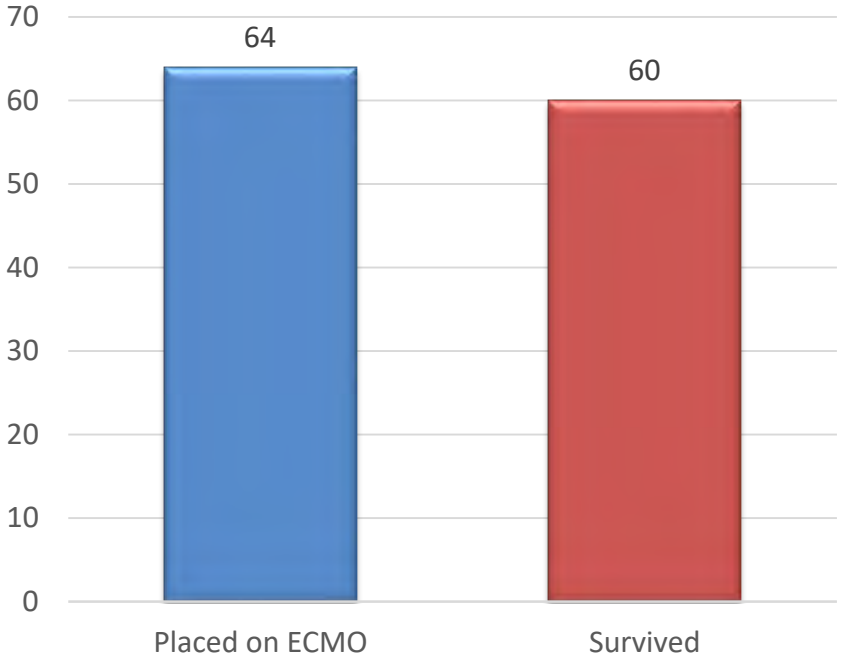
Figure 1: Distribution by Severity by Defect Size
Frequency %
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
13%
11%
18%
32%
40%
27%
28%
12%
A
B
C
D
JHACH
CDH Registry

Risk Stratifier	All CDH (n=101) Mean (SD)	No ECMO (n=37) Mean (SD)	ECMO (n=66) Mean (SD)
APGAR 1 min	3.35 (2)		
APGAR 5min	5.94 (2)		
CDH SG Predicted Survival	60.7 (21)		
LHR	1.06 (0.4)		
o/e LHR	36 (15)		
MRI-1 TFLV o/e	27 (13)		
MRI-2 TFLV o/e	24.5 (9)		
PH	7.07 (0.19)		
PCO2	91 (36)		
PO2	77 (101)		
Lactate	3.3 (3.65)		

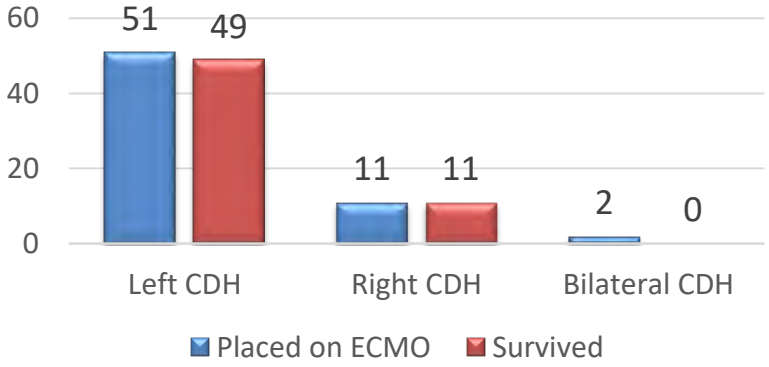
Risk Stratifier	All CDH (n=101) Mean (SD)	No ECMO (n=37) Mean (SD)	ECMO (n=66) Mean (SD)
APGAR 1 min	3.35 (2)	4.8 (2)	
APGAR 5min	5.94 (2)	7.1 (1.7)	
CDH SG Predicted Survival	60.7 (21)	76.5 (12)	
LHR	1.06 (0.4)	1.36 (0.54)	
o/e LHR	36 (15)	47 (18)	
MRI-1 TFLV o/e	27 (13)	40.4 (12)	
MRI-2 TFLV o/e	24.5 (9)	28.8 (6.8)	
PH	7.07 (0.19)	7.24 (0.13)	
PCO2	91 (36)	61.5 (24)	
PO2	77 (101)	131 (146)	
Lactate	3.3 (3.65)	1.8 (0.8)	

Risk Stratifier	All CDH (n=101) Mean (SD)	No ECMO (n=37) Mean (SD)	ECMO (n=66) Mean (SD)
APGAR 1 min	3.35 (2)	4.8 (2)	2.5 (1.5)
APGAR 5min	5.94 (2)	7.1 (1.7)	5.2 (1.8)
CDH SG Predicted Survival	60.7 (21)	76.5 (12)	51.6 (19.8)
LHR	1.06 (0.4)	1.36 (0.54)	0.93 (0.28)
o/e LHR	36 (15)	47 (18)	31 (10)
MRI-1 TFLV o/e	27 (13)	40.4 (12)	22 (8)
MRI-2 TFLV o/e	24.5 (9)	28.8 (6.8)	23 (9)
PH	7.07 (0.19)	7.24 (0.13)	6.97 (0.14)
PCO2	91 (36)	61.5 (24)	108 (30)
PO2	77 (101)	131 (146)	45 (32)
Lactate	3.3 (3.65)	1.8 (0.8)	4.0 (4.2)

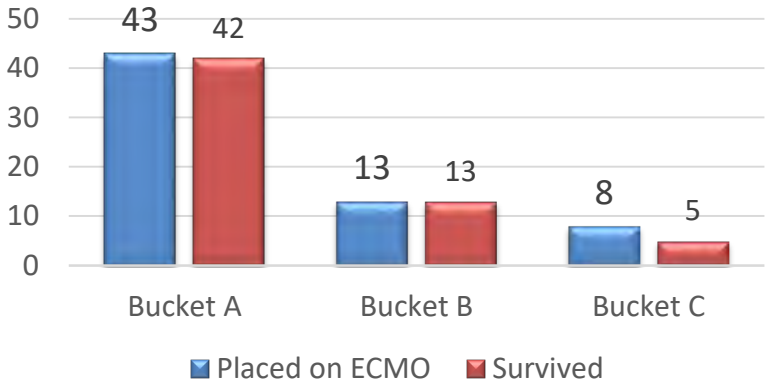
ECMO Survival to D/C



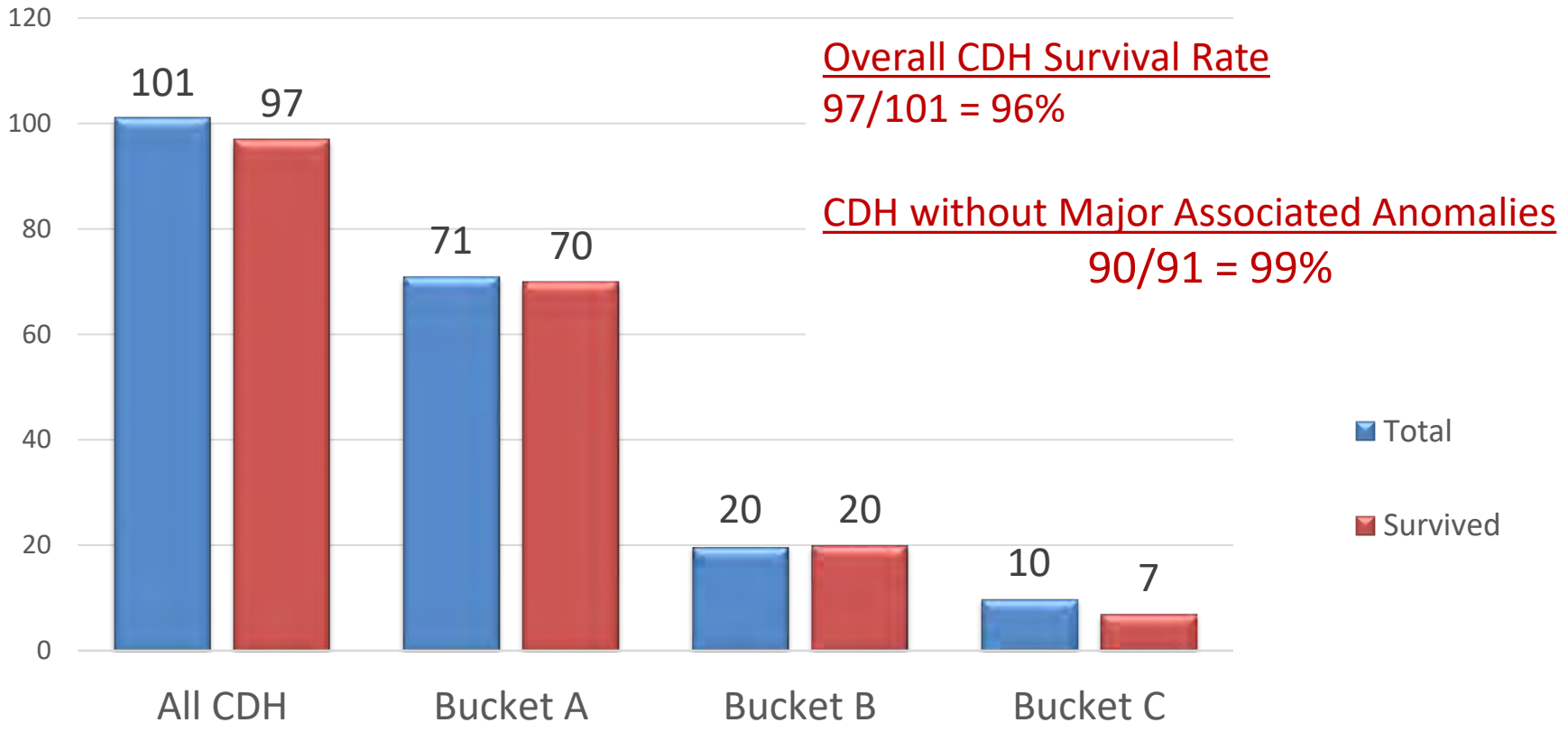
CDH-ECMO Anatomy



Buckets

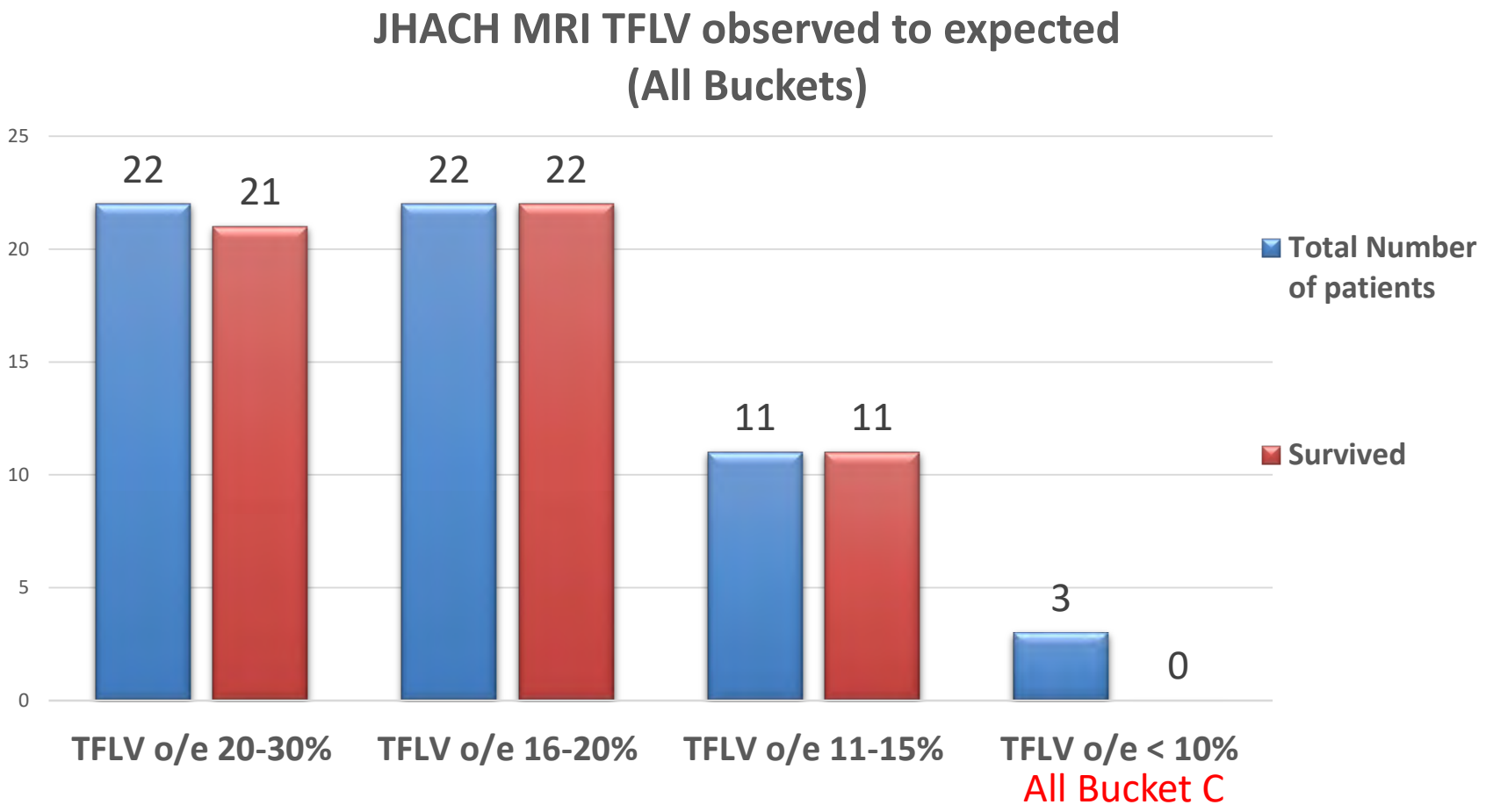


JHACH CDH Survival



Overall CDH Survival Rate
97/101 = 96%

CDH without Major Associated Anomalies
90/91 = 99%


JHACH MRI TFLV observed to expected
(All Buckets)
25
20
15
10
5
0
22
21
22
22
11
11
3
0
Total Number of patients
Survived
TFLV o/e 20-30%
TFLV o/e 16-20%
TFLV o/e 11-15%
TFLV o/e < 10%
All Bucket C

Time in Hospital

- No ECMO
- Extubation: 12.7 (+/- 6 days)
- Discharge: 1.5 mos (+/- 0.9)

- ECMO
- Extubation: 32 (+/- 33) days
- Discharge: 2.42 (+/- 2.2) mos

95/ 97 went home breathing spontaneously

2 tracheostomies, both from Bucket C

What we've learned

- Focus on the lungs
- Repair the CDH
- Do exceptional ECMO
- Believe they can survive

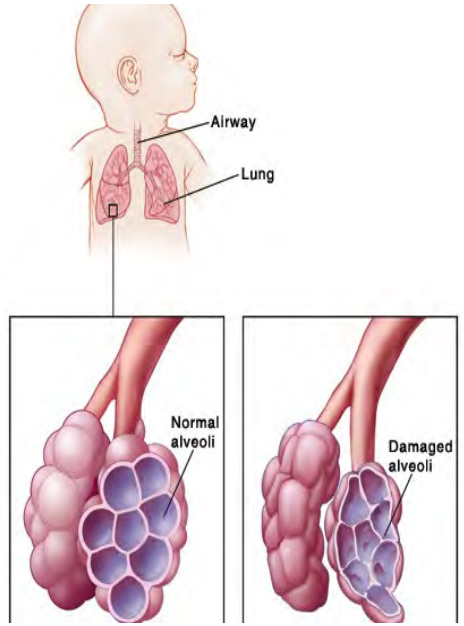
What we've learned

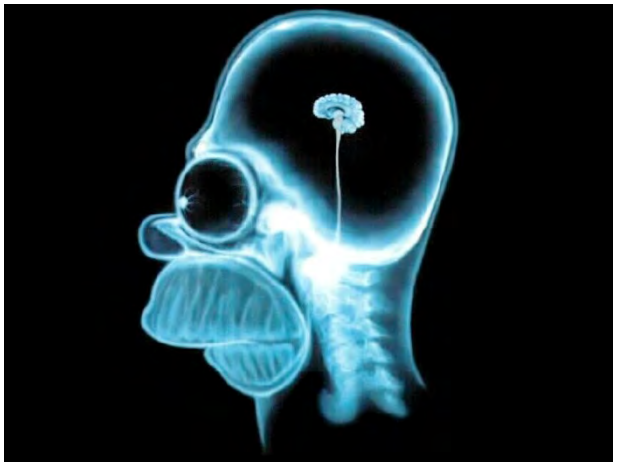
- Pulmonary hypoplasia in CDH needs not be lethal
- We currently have the tools necessary for exceptional outcomes.
- Survival in CDH without major associated anomalies can approach **100%**

- We can look prenatal patients in the eye and quote 95% predicted survival

CDH

- **Quantity of Survival**
  - **Care of lungs**
- **Quality of Survival**
  - **Care of brain**
- **(Another talk)**






Welcome to the CDH Family Reunion
all we do for kids


D.O.N.T.
FLOCK WITH THE FILTHY FLAMINGOS


BEACH
Sun, Sand & CDH
Help us Capture the fund
#Leston
Hope starts here!
all we do for kids

JOHNS HOPKINS
All Children's Hospital

all we do. all for kids.™