

### Viewing Time

The program will take up to one hour to complete.

### Target Audience

This program is designed for primary care physicians.

Other health care professionals working with patients and their families may also find this program of interest.

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### Faculty Disclosure

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### Management of Borderline Left Heart Structure/EFE

*28<sup>th</sup> Annual Katkov-Lundeen Visiting Professorship in Cardiology*

#### **Pedro del Nido, MD**

Professor of Surgery, Harvard Medical School;  
Chief, Department of Cardiac Surgery, Children's  
Hospital Boston, Boston, Massachusetts

### Management of Borderline Left Heart Structure/EFE

*28<sup>th</sup> Annual Katkov-Lundeen Visiting Professorship in Cardiology*

*A lecture about the different  
management options for neonatal  
HLHS.*

## Program Objectives

*Upon completion of this program, participants should be able to:*

- Inform participants of new developments in diagnosis and/or treatment of specific pediatric diseases
- Review current state-of-the-art approaches to common pediatric problems
- Present new information about changes in pediatric illness and newly recognized conditions affecting children

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## Receiving CME Credit

To receive CME credit you must view the entire program and complete the evaluation form at the end.

## Management of the Borderline Left Heart

Pedro J. del Nido, M.D.  
Department of Cardiac Surgery  
Children's Hospital - Boston




## HLHS

- Underdevelopment of left heart structures
- Aortic +/- mitral stenosis or atresia
- Etiology unknown but Ao valve obstruction suspected in large subgroup
- Managed as a single anatomic defect

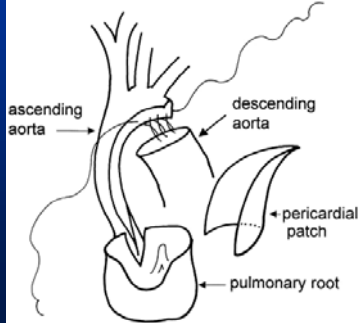


### HLHS: Single ventricle management

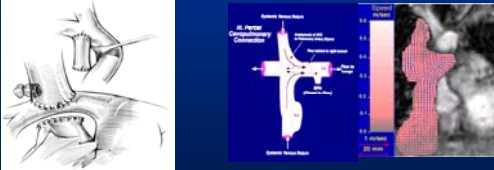
- Staged palliation
  - Arch reconstruction
  - Stansel connection
  - Atrial septectomy
  - Ao/RV to PA shunt
- Intercurrent mortality
- Cavo-pulmonary connection
  - SVC
  - IVC



### HLHS: 1<sup>st</sup> stage palliation – arch reconstruction



### HLHS: Cavo-pulmonary connection

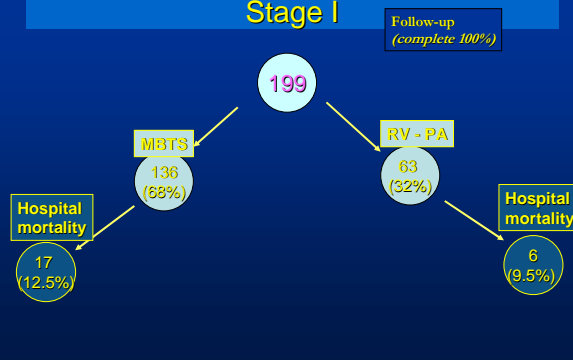


### Surgical Management of HLHS 199 pts. (Jan 2001 – Dec 2005)

- HLHS: 147 (74%)
  - AS / MS: 62
  - AA / MA: 45
  - AA / MS: 33
  - AS / MA: 7
- Restrictive PFO: 18 (9%)
- Intact atrial septum: 6 (3%)
- Other diagnoses: 52 (26%)

### Surgical Management of HLHS: Stage I


Follow-up (complete 100%)



```

    graph TD
      A((199)) --> B((136 MBTS 88%))
      A --> C((63 RV-PA 32%))
      B --> D((17 Hospital mortality 12.5%))
      C --> E((6 Hospital mortality 9.5%))
  
```

### Inter-stage Results

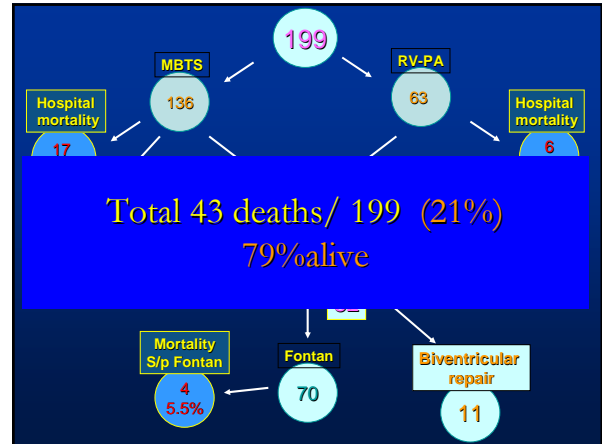
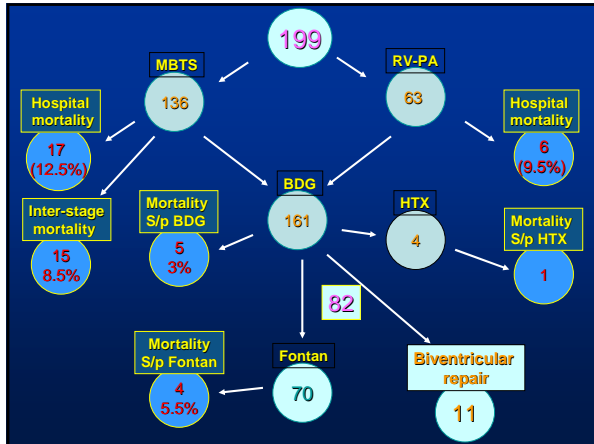


Overall inter-stage mortality: 15 / 176 (8.5%)

- MBTS 15 / 119 (12.6%)\*
- RV-PA 0 / 57 (0%)

Mean Time to BDG: 163 ± 60 days

	MBTS	RV-PA	p
Days	178 ± 60	137 ± 51*	0.0001



### Alternative Management of HLHS: Fetal intervention

Allan Sharland Tynan 1989

The natural history of the hypoplastic left heart syndrome.

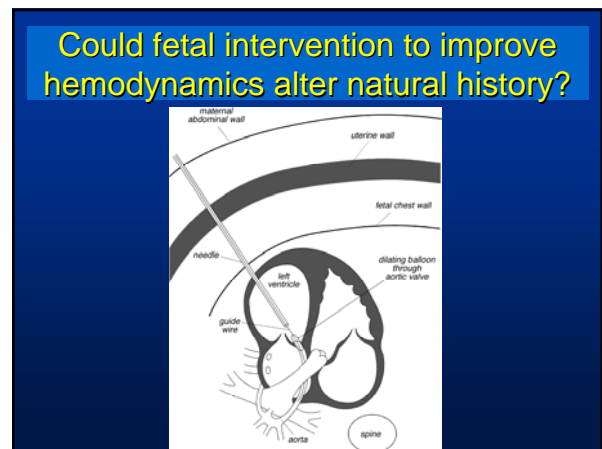
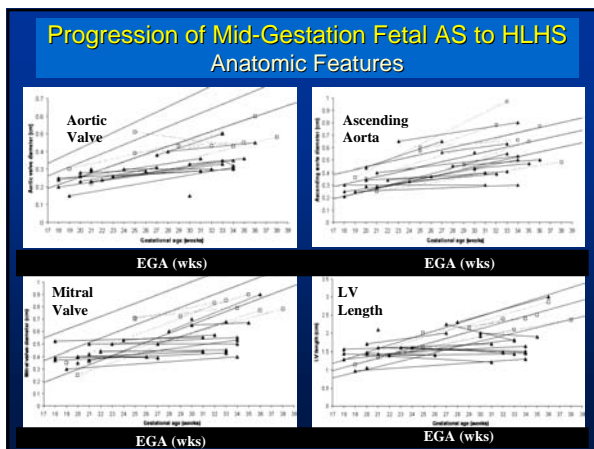
Allan I.D. Sharland G. Tynan MD  
Department of Perinatal, Guy's Hospital, London, U.K.

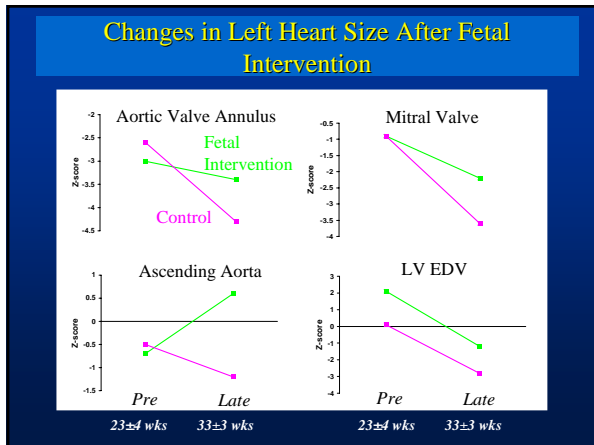
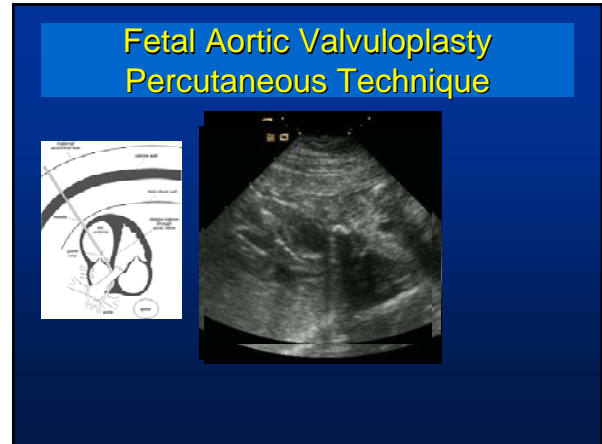
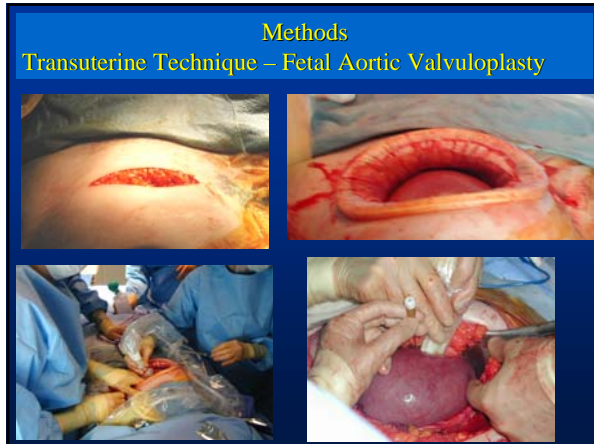
In a fetus, examined initially at 22 weeks gestation, we identified the echocardiographic features of a dilated, hypertrophied and poorly contracting left ventricle. The presumptive diagnosis was critical aortic stenosis. Subsequent scans at 32 weeks and at term showed that the left ventricle had not grown since the first study such that the left ventricle had developed the appearance of a hypoplastic and densely echogenic chamber. Thus, in some forms of the hypoplastic left heart syndrome, the left ventricle can be of normal size or even dilated in early pregnancy. This may mean that the more subtle signs of poor left ventricular contraction could be overlooked in a routine four-chamber view obstetric scan.

### Natural History of Fetal Aortic Stenosis

#### Typical Progression

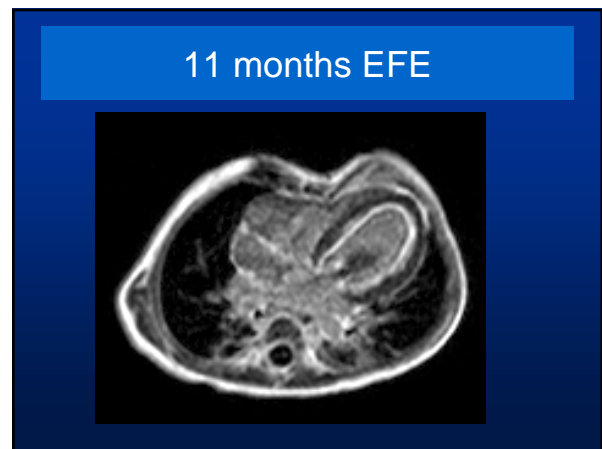
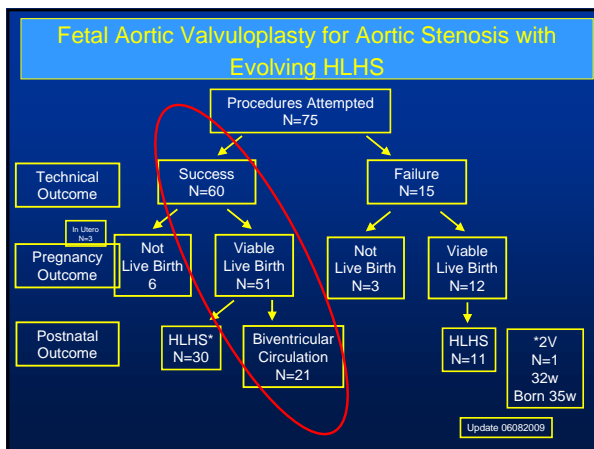
22w Dilated LV      34w HLHS



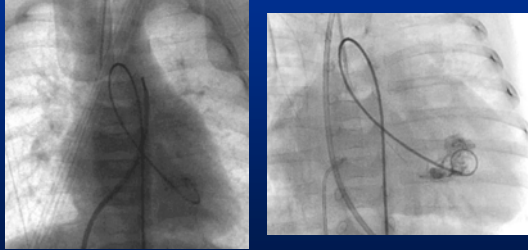


### Changes in Left Heart Function After Fetal Intervention

Variable	Pre-dilation 23.5±2.1 wks	Post-dilation 32.8±2.8 wks	P
Antegrade flow in TAA	0/15 (0%)	11/16 (69%)	<0.001
PFO bidirectional flow	0/16 (0%)	4/16 (25%)	0.05
Biphasic MV inflow	1/14 (7%)	13/14 (93%)	<0.001
LV ejection fraction (%)	19 ± 10	41 ± 16	<0.001



### Borderline Left Heart: Aortic and mitral stenosis

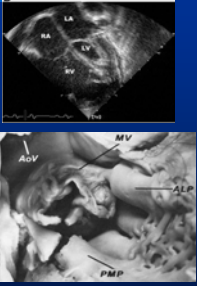


### Left Heart Disease / Borderline left heart

- Characteristics
  - Mild LV hypoplasia
  - Mitral stenosis
  - Aortic stenosis/regurgitation
  - Endocardial fibroelastosis
  - Diastolic and systolic dysfunction


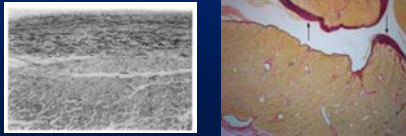
Single Ventricle Palliation

Biventricular Repair  
Aortic / MV repair  
Coarctation repair



### Endocardial Fibroelastosis

- Fibrotic thickening of endocardium
- Histology – prominent elastic fibers
- Etiology
  - Primary – X linked, hereditary
  - Secondary – left heart obstruction
- Prevents LV growth, relaxation

### Left Ventricular Rehabilitation is Effective in Maintaining Two-Ventricle Physiology in the Borderline Left Heart

Sitaram M. Emani, Emile A. Bacha, Doff B. McElhinney, Gerald R. Marx, Wayne Tworetzky, Frank A. Pigula, Pedro J. del Nido

Children's Hospital Boston, Boston, MA

### LV Rehabilitation

- Operative Techniques
  - EFE resection
  - Aortic valve repair
  - Mitral valve repair
- Primary – Performed to maintain 2V circulation
- Staged – Following 1V palliation

### EFE resection



### Mitral Valvuloplasty

- Papillary muscle splitting
- Secondary chord division
- Commissurotomy
- Debridement of thickened leaflets



### Study design

- Retrospective study, single institution, 2004-2008
- Patients with borderline left heart who
  - Failed initial attempts at biventricular repair
  - Underwent primary LV rehabilitation in infancy
- Preoperative and most recent (postoperative) echocardiogram and cardiac catheterization data recorded
- Left atrial pressures postoperatively measured from the intracardiac LA line were included in the comparison of LA pressure

### Patient characteristics

- 9 patients underwent primary LV rehabilitation
- 3 female
- Procedures prior to LV rehabilitation
  - 5 fetal balloon dilation of the aortic valve
  - 7 postnatal balloon dilation of the aortic valve
  - 3 patients underwent isolated coarctation / arch repair
- “Failed” biventricular circulation – symptoms / hemodynamics
- Median age at surgery = 5.6 months (range 19 days to 3 years)

### Preoperative hemodynamic data

- Preoperative data obtained at cardiac catheterization or echocardiography

Ejection Fraction (%)	36 ± 12
LV end-diastolic volume Z score	-0.18 ± 0.03
Aortic valve Z score	-1.6 ± 0.4
Mitral valve Z score	0.5 ± 0.6
LV end-diastolic pressure (mmHg)	22 ± 2.4
Left atrial pressure (mmHg)	28 ± 2.4
Right ventricular pressure (mmHg)	70 ± 18
UVR-SA score (CHSS)	6.1 (-15 to 24)

### Intraoperative details

	N=
MV repair	9
Separation of fused papillary muscle	9
Division of secondary chordae	7
Commissurotomy	3
Leaflet thinning	5
LV EFE resection	9
Aortic Valve repair	4
Subaortic resection	2
Fenestrated ASD closure	3

### Results

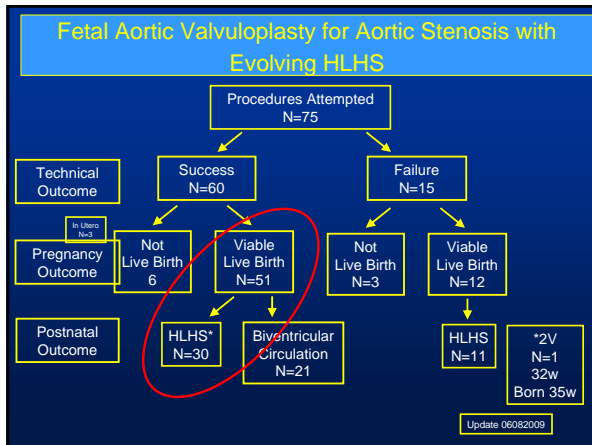
- There was no operative mortality
- Median follow up 25 months (6 mo to 10 yrs)
- One late death from non cardiac causes (motor vehicle collision)
- 2 patients required reinterventions:
  - 1 patient required 2 procedures for mitral valve replacement
  - 1 aortic and mitral valve repairs
- No patients required single ventricle palliation or heart transplantation

### Postoperative hemodynamics / LV morphology

	Preoperative	Recent follow up	P value
Echocardiogram			
Ejection fraction (%)	36 ± 12	58 ± 10	<0.01
LVEDV z score	-0.2 ± 1.7	2.7 ± 1.8	<0.05
LV mass:volume ratio Z score	0.7 ± 1.2	0.1 ± 2.1	NS
Aortic valve gradient (mmHg)	39±22	28±19	NS
Mitral valve gradient (mmHg)	7±3	5±2	NS
RV:LV systolic pressure ratio	0.78±0.36	0.32 ± 0.11	<0.05
Cardiac catheterization or intracardiac line			
LA pressure (mmHg)	27.5±6.3	11.0 ± 2.4*	<0.01

### Summary

- In patients with borderline left heart who fail biventricular physiology, primary LV rehabilitation allows maintenance of biventricular circulation
- Intermediate term improvement in RV pressures, LV ejection fraction



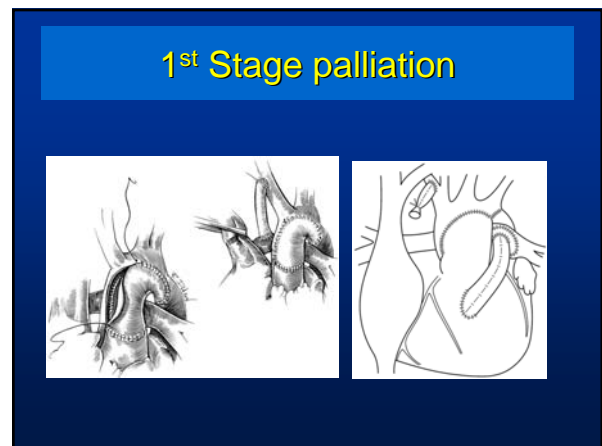
### Neonatal HLHS after Fetal Intervention for Aortic Stenosis

Fetal Procedure	Tech Successful N=30	Tech Unsuccessful N=11
Pre St 1 mortality	N=1 Sepsis	N=0
St 1 mortality	2/28 1/1 Tx*	1/11
Further mortality	1/27 Tx*	1/10

HLHS Group Current Survival 24/31 = 77% (range 0.5 - 8 years)

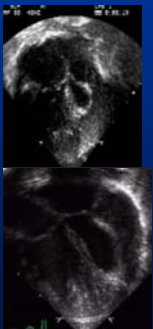
### Hypothesis

- EFE limits LV growth post fetal intervention
- LV has potential for growth post-natally
- EFE resection + mitral/aortic valvotomy will permit "catch-up" growth after birth
- Ao valvot. can improve LV dysfunction

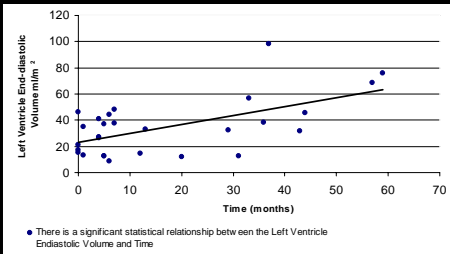


### Resection of EFE

- Can be resected
- Does not appear to recur
- Post-natal LV "catch-up" growth does occur



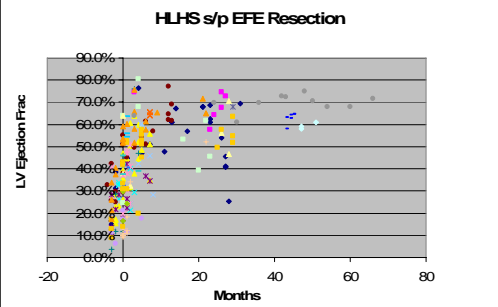
### LV end diastolic volume (MRI)



P value = .000917

### Progression of LV function in BLH post EFE resection

HLHS s/p EFE Resection




Group	Stage 1	BDG / LV rehab	Fontan / LV rehab	Deaths	Median f/u
LV Rehab Group (n=27)	27 Patients	25 Patients	7 Patients	3 (11%)	17 mo (4-68)
Traditional SVP (n=35)	35 Patients	30 patients	24 patients	7 (20%)	43 mo (8-146)

Flowchart details: In the LV Rehab Group, Stage 1 leads to 27 patients. From Stage 1, 2 patients go to BDG/LV rehab, 1 to Death, and 24 go to Fontan/LV rehab. From BDG/LV rehab, 1 patient goes to Death and 24 go to Biventricular conversion. From Fontan/LV rehab, 5 patients go to Biventricular conversion. In the Traditional SVP group, Stage 1 leads to 35 patients. From Stage 1, 5 patients go to BDG, 2 to Death, and 28 go to Fontan. From BDG, 2 patients go to Death and 28 go to Fontan. From Fontan, 24 patients remain in Fontan and 4 go to Biventricular conversion.

### Conclusions: Clinical Studies

LV function and size can be recovered

- Time scale > 2-3yrs
- Systolic function-maintained
- Ao/mitral valve intervention- common



### Endocardial Fibroelastosis



## Immunohistology of EFE

- composition of cells in EFE
- Alpha smooth muscle actin (red) and actin (green). Nuclei are labeled with DAPI.

**nature  
medicine**

### Endothelial-to-mesenchymal transition contributes to cardiac fibrosis

Elisabeth M Zeisberg<sup>1</sup>, Oleg Tarnavski<sup>2</sup>, Michael Zeisberg<sup>1</sup>, Adam L Dorfman<sup>3</sup>, Julie R McMullen<sup>4</sup>, Erika Gustafsson<sup>5</sup>, Anil Chandrasekhar<sup>6</sup>, Xueli Yuan<sup>6</sup>, William T Pu<sup>3</sup>, Anita B Roberts<sup>7</sup>, Eric G Neilson<sup>8</sup>, Mohamed H Sayegh<sup>9</sup>, Seigo Izumo<sup>2</sup> & Raghu Kalluri<sup>1,9,10</sup>

## Conclusions: Histology

- The cells isolated from EFE express high amounts of alpha smooth muscle actin (SMA), vimentin – a mesenchymal marker
- Both TGFbeta 1 and 2, the known EMT inducers, fail to increase the SMA expression
- Cells composing EFE are terminally differentiated myofibroblasts
- May be result of EMT earlier (fetal stage)

## Valvulogenesis vs EFE etiology?

**Signaling network model for heart valve development and remodeling**

# Thank You

## Comments and Questions

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