Principles of Cardiac Development

A help or a hindrance? to our understanding of Double Outlet Right Ventricle (DORV)

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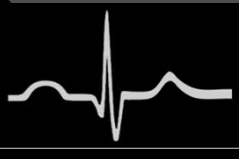
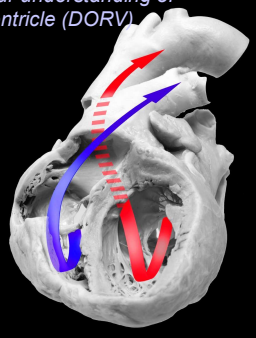
Utrecht, January 2025





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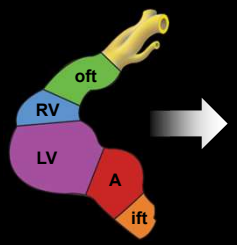
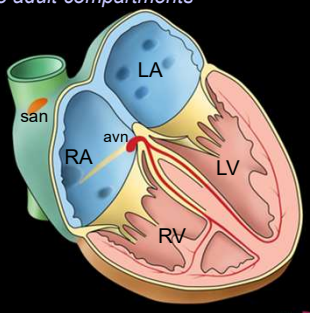
Recent Past

The cardiac tube is a segmented tube containing the precursors for the adult compartments





Many medical textbooks

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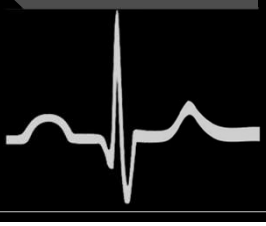
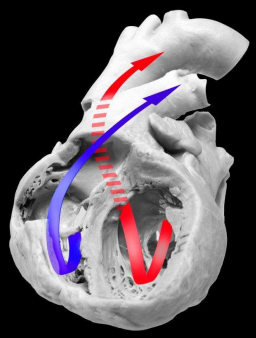
Principles of Cardiac Development

Important topics

1. *Cardiac growth*
2. *Chamber formation*
3. *DORV*





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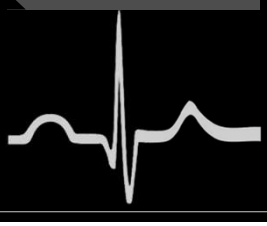

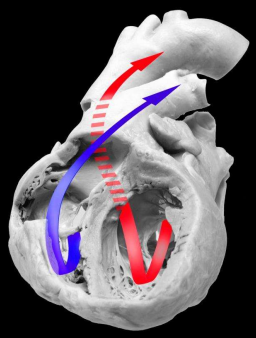

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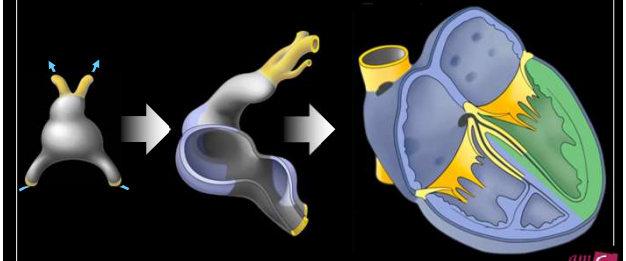
The tubular heart contains little more than the precursors for the left ventricle; growth by addition of cells at the venous & arterial poles

May be even less



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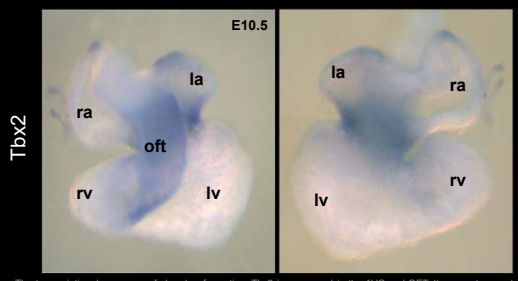
The power of lineage studies

Irreversible molecular labeling of cells of the OFT and AVC allows following the fate of these cells at later stages



The transcriptional repressor of chamber formation Tbx2 is expressed in the AVC and OFT. Its promotor can be used to irreversibly label the myocardial cells of OFT and AVC and their offspring. (Aanhaanen et al, Circ Res 104(2009)1267)

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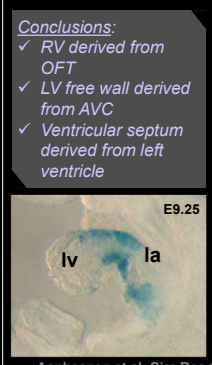
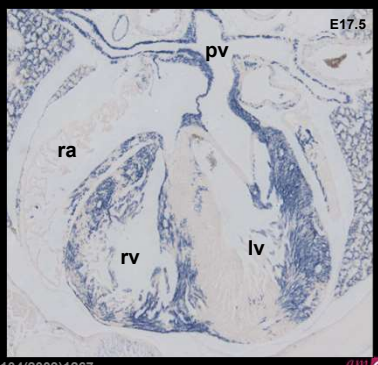
The power of lineage studies

Conclusions:
- ✓ RV derived from OFT
- ✓ LV free wall derived from AVC
- ✓ Ventricular septum derived from left ventricle





Aanhaanen et al, Circ Res 104(2009)1267

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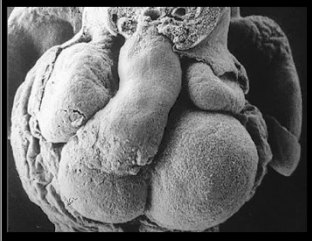
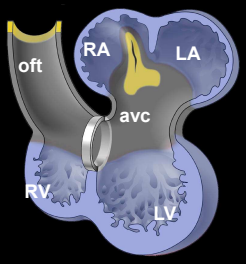
Development of the chambers in the tubular heart



Bob Anderson: dog-leg band



human 38 days ventral view ***Ballooning model***

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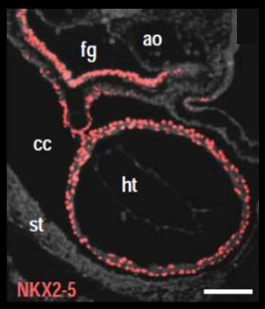
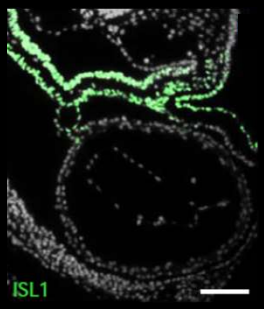
Early cardiac growth

(human Carnegie stage 10; ~ 3 weeks of development)





Sizarov et al, Circulation 123(2011)1125

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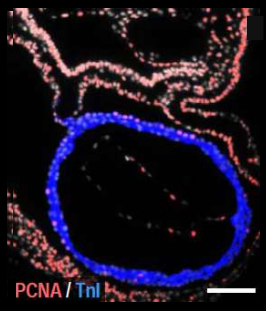

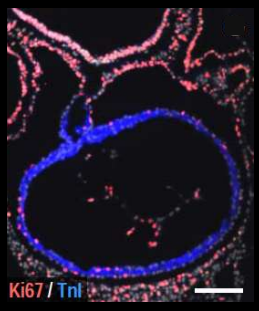

Sizarov et al, Circulation 123(2011)1125

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Early cardiac growth

(human)

Sizarov et al, Circulation 123(2011)1125
Van den Berg et al, Circ Res 104(2009)179

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Principles of Cardiac Development

Summary 1

Cardiac Growth

- ✓ Upon overt differentiation into cardiac muscle cells forming the cardiac tube, proliferation ceases
- ✓ The entire dorsal coelomic wall is highly proliferative, Isl1-positive and contributes to both pharyngeal wall and heart; it is called: cardio-pharyngeal mesoderm
- ✓ The cardiac precursor pool that gradually is added to the heart is called second heart field

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Summary 2

Cardiac Growth and
DOUBLE OUTLET RIGHT VENTRICLE (DORV)

- ✓ Impairment of the addition of cells to the OFT leads to a variety of OFT malformations, including DORV
- ✓ Imbalance between the left and right sided addition of cells also leads to a variety of OFT malformations, including DORV
- ✓ Obviously, a combination of both processes makes the spectrum even more complex

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Summary 3

Cardiac defects are due to defects in the development of the second heart field

- ✓ Because the embryo quickly becomes dependent on circulation, serious defects of the early heart tube (**primary heart field**) are lethal.
- ✓ Consequently, structural congenital malformations of the heart observed in viable fetuses are typically associated with the development of the **second heart field**.
- ✓ Defects in proteins of the contractile apparatus, energy metabolism, ion transport or calcium handling, constitute another category of malformations.

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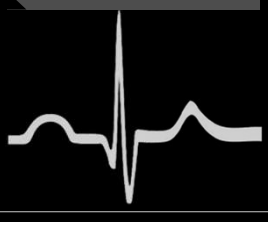

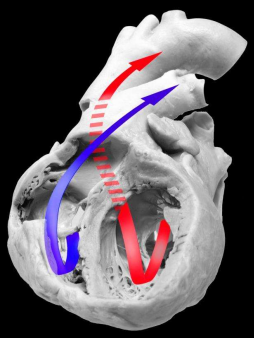

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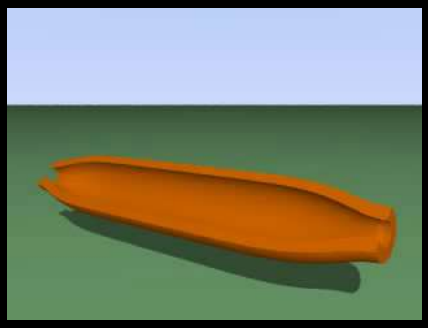
Animation of the pattern of contraction of the primary heart tube



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Basic myocardial features differ between primary and developing chamber myocardium

Feature	Primary Embryonic Myocardium	Atrial & Ventricular Chamber Myocardium
Automaticity	High (Hcn4)	Low
Conduction	Low (Cx45)	High (Cx40/43)
Contractility	Slow	High
SR activity	Slow	High
Proliferation	Slow	High*

* Only before birth

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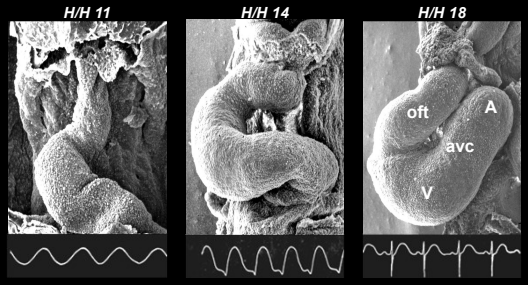
The development of the electrocardiogram betrays the formation of fast-conducting chambers



EM: Sc Virágh
ECG: G. Steding

chicken

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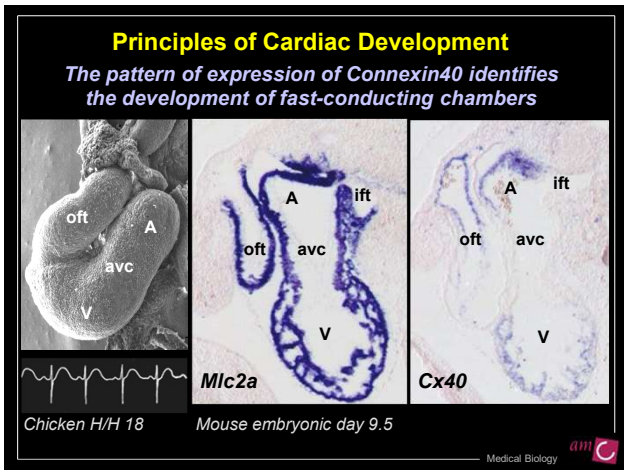

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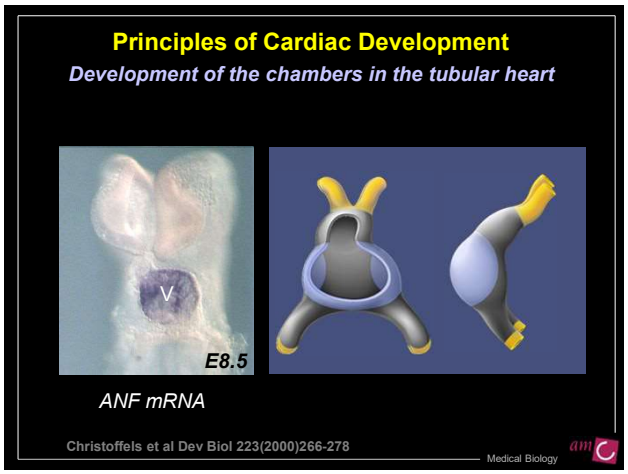

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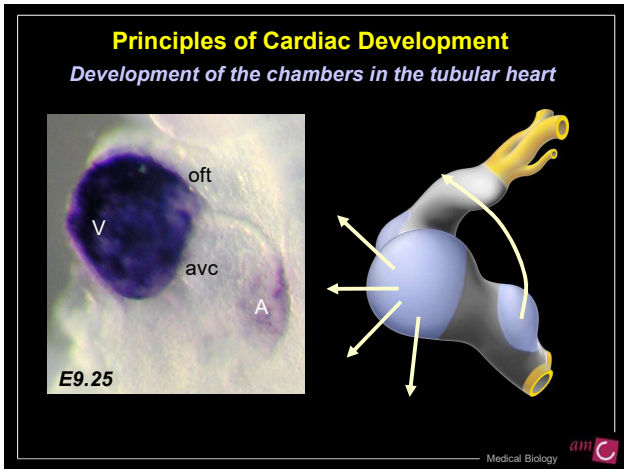

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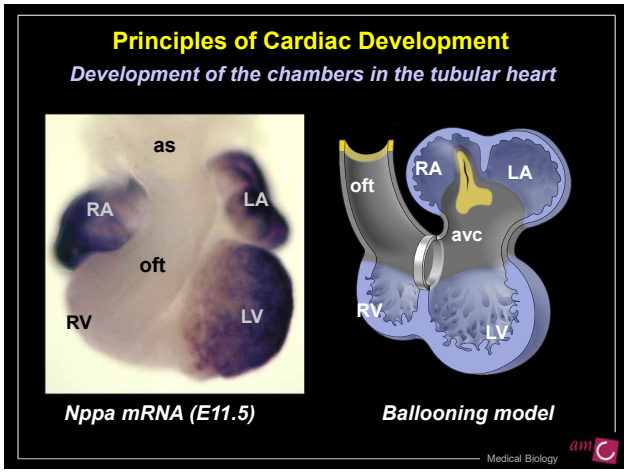

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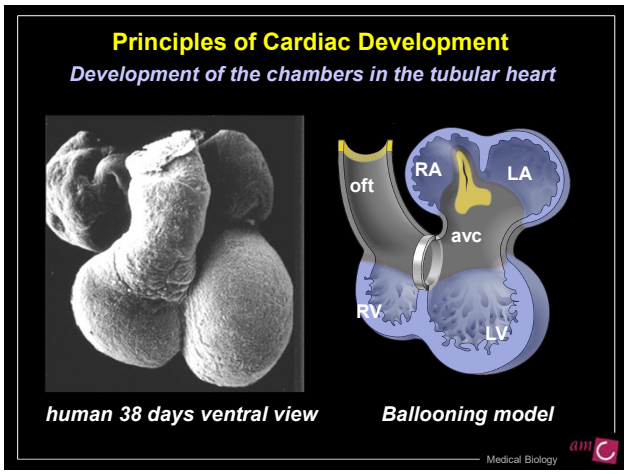

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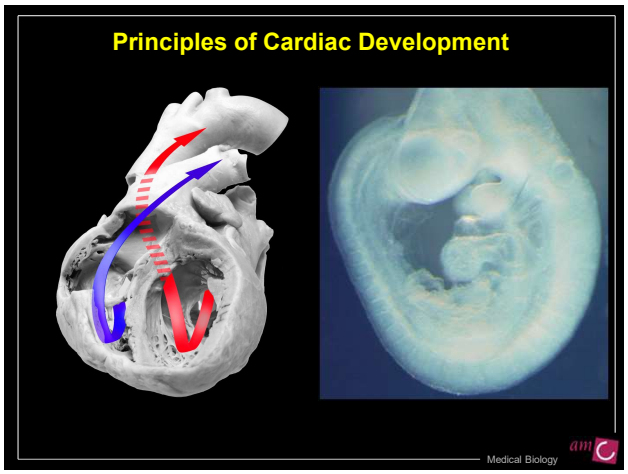

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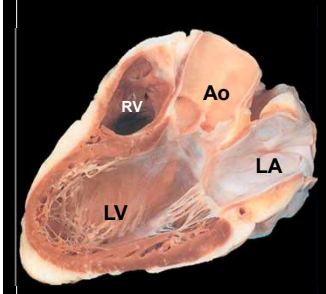

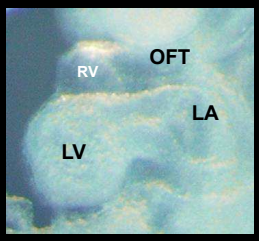

AE Becker and RH Anderson Cardiac Anatomy, 1981

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Summary 4

Cardiac Chamber Formation

- ✓ The primary heart tube consists of structurally poorly developed muscle cells, with high automaticity along the entire tube
- ✓ The dominant pacemaker always is at the venous pole of the heart, which results in unidirectional contraction waves
- ✓ The regional development of fast-conducting & fast-contracting chambers, which remain flanked by slow-conducting & long-contracting primary myocardium, explains the ECG and cardiac functioning without valves
- ✓ This design is evolutionary conserved

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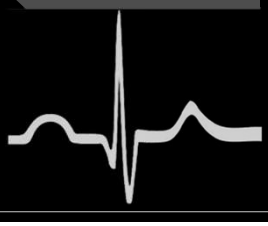
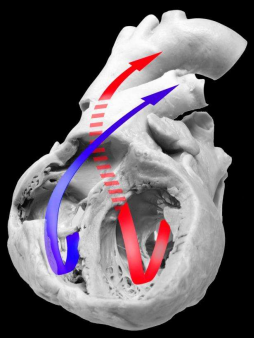
Important topics

1. *Cardiac growth*
2. *Chamber formation*
3. *DORV*





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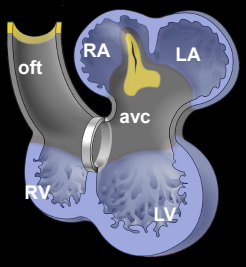
Remodelling at the inner curvature aligns the chambers

human 38 days ventral view



Ballooning model

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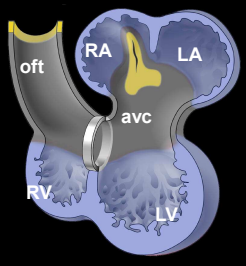
human 38 days dorsal view



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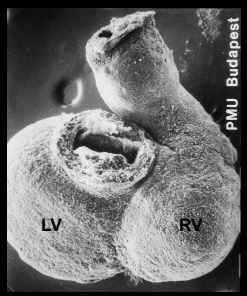

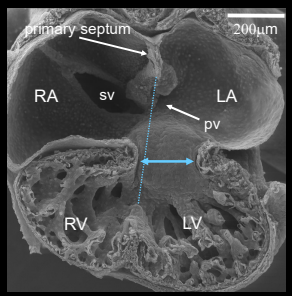

Courtesy Nigel Brown

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Principles of Cardiac Development

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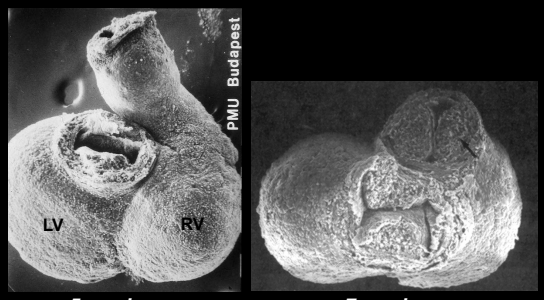

5 weeks *7 weeks*

Courtesy Szabolcs Virágh

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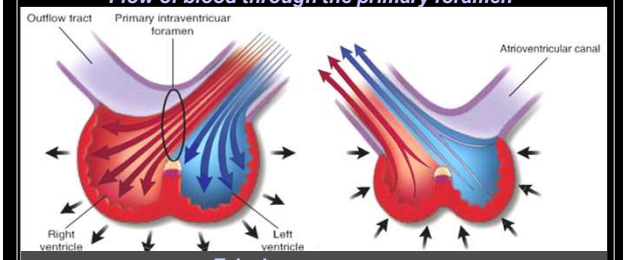
Flow of blood through the primary foramen



Take home messages:

1. The primary foramen is the *inlet for right* and the *outlet for left*
2. The primary foramen will not close, but become divided by the membranous septum

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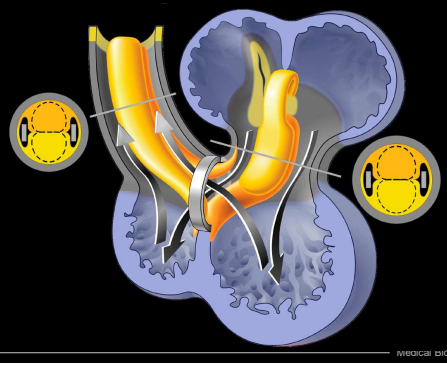
Physical separation between left and right flows of blood



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Double outlet right ventricle (DORV)

Classification

- ✓ DORV is but a description of the ventriculo-arterial connections
- ✓ It can co-occur with almost all other defects in cardiac development
- ✓ Differentiation/classification based on morphology interventricular communications and arterial conus

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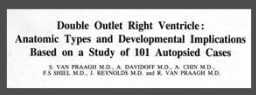
Double outlet right ventricle (DORV)

Leading classifications

- ✓ IPPC classification

- ✓ Richard van Praagh



- ✓ Maurice Lev

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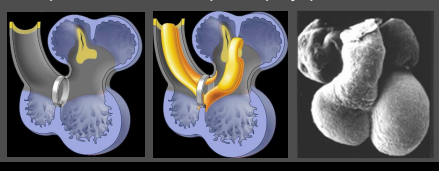
Double outlet right ventricle (DORV)

Classification according to van Praagh

- ✓ Group I: DORV with mainly conotruncal anomalies
- ✓ Group II: DORV with conotruncal anomalies and malformations of the AV-valve and ventricles
- ✓ Group III: DORV with asplenia/polysplenia



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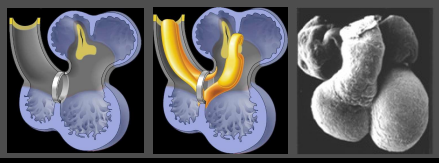

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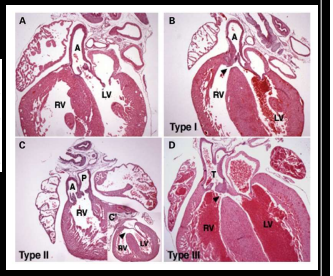
Tbx1 hypomorphs display variable phenotypes including DORV

Table 3. Cardiac outflow tract phenotype variation in E18.5 embryos

% Tbx1 activity	n	Normal	Type I VSD	Type II DORV	Type III Inc. TA	Type IV TA
34	15	15	0	0	0	0
18	13	2	5	1	2	3
15	23	0	0	2	16	5
4	14	0	0	0	0	14



Zhang & Baldini, 2008, Hum Mol Gen

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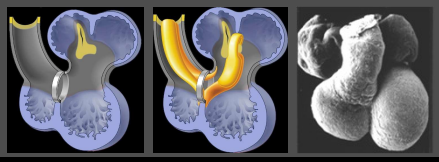

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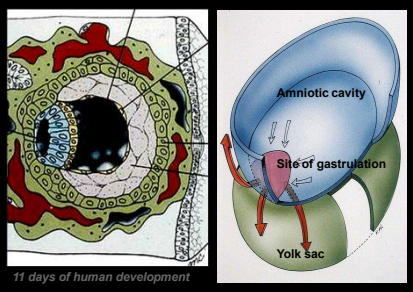
During GASTULATION the right / left body axis is established

Lewis Wolpert: *it is "not birth, marriage or death, but gastrulation which is truly the most important time in life*



11 days of human development

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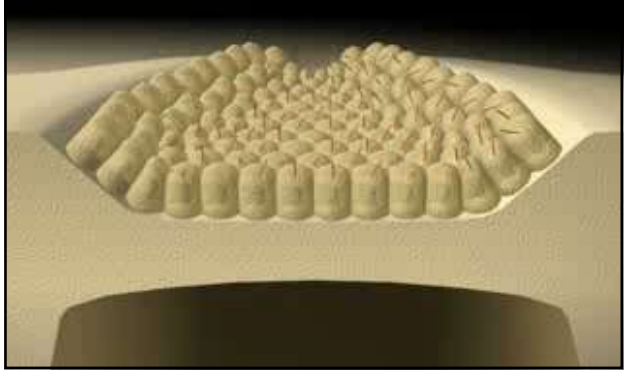
Principles of Cardiac Development

Development of the left-right axis



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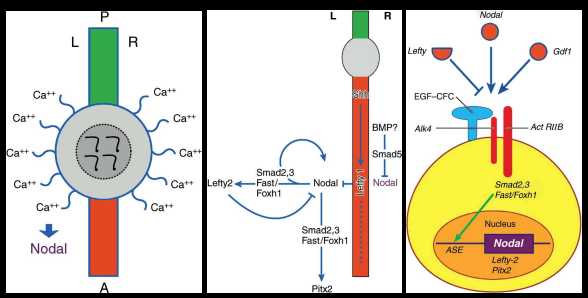
Principles of Cardiac Development

Development of the left-right axis



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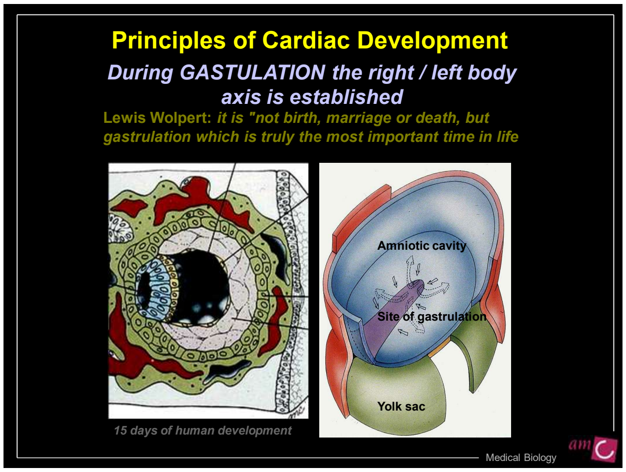
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During GASTULATION the right / left body axis is established
Lewis Wolpert: it is "not birth, marriage or death, but gastrulation which is truly the most important time in life
Amniotic cavity
Site of gastrulation
Yolk sac
15 days of human development
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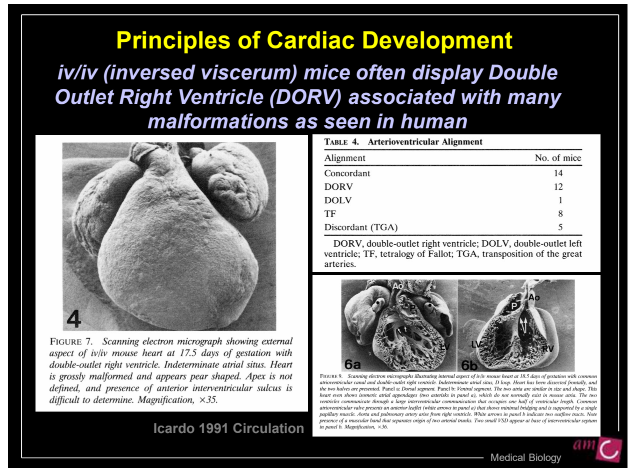
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iv/iv (inversed viscerum) mice often display Double Outlet Right Ventricle (DORV) associated with many malformations as seen in human
TABLE 4. Arterioventricular Alignment
Alignment No. of mice
Concordant 14
DORV 12
DOLV 1
TF 8
Discordant (TGA) 5
DORV, double-outlet right ventricle; DOLV, double-outlet left ventricle; TF, tetralogy of Fallot; TGA, transposition of the great arteries.
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FIGURE 7. Scanning electron micrograph showing external aspect of iv/iv mouse heart at 17.5 days of gestation with double-outlet right ventricle. Indeterminate atrial situs. Heart is grossly malformed and appears pear shaped. Apex is not defined, and presence of anterior interventricular sulcus is difficult to determine. Magnification, ×35.
6a
6b
Ao
LV
RV
Icardo 1991 Circulation
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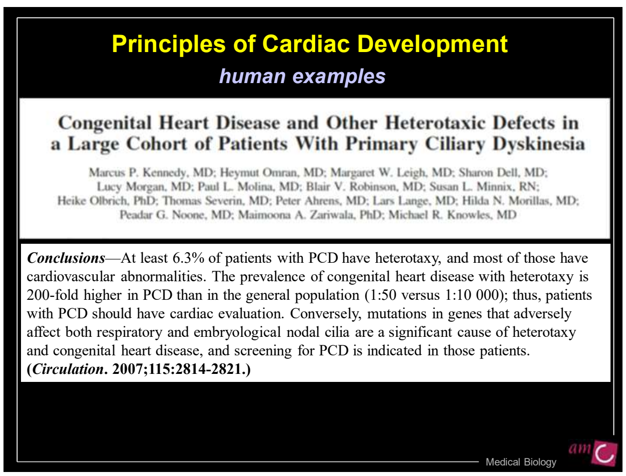
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human examples
Congenital Heart Disease and Other Heterotaxic Defects in a Large Cohort of Patients With Primary Ciliary Dyskinesia
Marcus P. Kennedy, MD; Heymut Omran, MD; Margaret W. Leigh, MD; Sharon Dell, MD; Lucy Morgan, MD; Paul L. Molina, MD; Blair V. Robinson, MD; Susan L. Minnix, RN; Heike Olbrich, PhD; Thomas Severin, MD; Peter Ahrens, MD; Lars Lange, MD; Hilda N. Morillas, MD; Peadar G. Noone, MD; Maimoona A. Zariwala, PhD; Michael R. Knowles, MD
Conclusions—At least 6.3% of patients with PCD have heterotaxy, and most of those have cardiovascular abnormalities. The prevalence of congenital heart disease with heterotaxy is 200-fold higher in PCD than in the general population (1:50 versus 1:10 000); thus, patients with PCD should have cardiac evaluation. Conversely, mutations in genes that adversely affect both respiratory and embryological nodal cilia are a significant cause of heterotaxy and congenital heart disease, and screening for PCD is indicated in those patients. (Circulation. 2007;115:2814-2821.)
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Thanks
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