Coronary pathology in children

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Coronary arteries in animals

“Not everyone has coronary vessels”

- Invertebrates: no
- Amphibians: no

- Vertebrates: mammals, reptiles, avians: yes
  - common characteristics: pulmonary respiration and no percutaneous respiration

- Fish: coronary arteries only in:
  - Larger, fast-swimming, predatory
  - Living in poorly oxygenated environment

Reese DE, Circ Res 2002; 91: 761-8
Development of coronary arteries: late event in cardiac morphogenesis

- Endocardial cushions
- Tricuspid gully
- Elongation of cardiac outflow tract
- Aortic arches 4 and 6
- Semilunar valves development
- Delamination of tricuspid valve
- Convergence
- Elongation of cardiac outflow tract
- Aortic arches 4 and 6
- Looping
- Wedging
- Cardiac septation
- Right horn of sinus venosus
- Primitive pulmonary vein
- Aortic arches 2 and 3

Day

- 18
- 23
- 30
- 40
- 42
- 44
- 50

Connection coro-aorta
Coronary artery patterning in \( Tbx1^{-/-} \) hearts

\[ Tbx1^{+/-}\]

Connexin40 eGFP

\[ Tbx1^{+/-}\]

\[ Tbx1^{-/-}\]
Coronary artery patterning in $Tbx1^{-/-}$ hearts

$Tbx1^{+/−}$

$Tbx1^{-/-}$
Coronary sinuses are formed via ingrowth of the peritruncal capillary plexus

Hypoxia and apoptosis are correlated with the invasion of the Aorta

Tomanek RJ, Angiogenesis, 2005
Embryology: the coronary arteries enter the aorta

• The coronary arteries are « attracted » by the aorta (subaortic domain)
• They enter the aorta to the nearest point of their epicardial course
• While avoiding the pulmonary artery (myocardial subpulmonary domain)
Embryology: coronary artery patterning

- Coronary artery patterning also depends on the underlying ventricle (double discordance)
- L-loop: mirror-imaged coronary arteries
Conotruncal defects

- The location of the coronary ostia depends on the degree of rotation of the outflow tract (which modifies the location of the subpulmonary domain)
Detection of myocardial ischemia in children
Figure 2 Real and ‘pseudo-real’ late gadolinium enhancement (LGE) in 3 patients with positive LGE studies. (Ai-iii) Genuine LGE is evident in the mid inferior wall in the 2-chamber view (Ai) with both linear (black arrows) and more focal (white arrow) enhancement. Confirmation of these findings is provided by short axis cross cuts through this region, which also show subendocardial (white arrows) and midwall nodular (dotted arrow) myocardial scar. (Bi-ii) “Pseudo” LGE (white arrow) is present at the site of ventricular septal defect (VSD) repair shown in 4-chamber (i) and short axis (ii) views. (C) “Pseudo” LGE (black arrow) evident in a large surgical patch placed for VSD repair.
Abnormal epicardial course of coronary arteries
Main abnormal epicardial courses of coronary arteries
Abnormal courses considered at low risk of cardiac event
Abnormal courses considered at high risk of cardiac event
Main abnormal epicardial courses
Interarterial course of coronary arteries

0.1% - 0.3% of the population (≈ 100,000 people in France)
Two anatomical variants

Interarterial course isolated

Interarterial course and intramural
Mechanism of myocardial ischemia
Basso C et al. JACC 2000

Sudden death mechanisms
- compression of inter arterial course during effort
- progressive stenosis of the inter arterial course: early atherosclerosis/remodeling/acute thrombosis
- subclinical ischemia with myocardial fibrosis and arrhythmias
Serendipitously diagnosed or not
Major Coronary Artery Anomalies in a Pediatric Population: Incidence and Clinical Importance

Julie A. Davis, MD, Frank Cecchin, MD, FACC, Thomas K. Jones, MD, FACC, Michael A. Portman, MD, FACC

Seattle, Washington

3/3150
0.09%

4/2388
0.17%
Left coronary artery from the right ostium with inter arterial course
Left coronary artery from the right ostium with inter arterial course
Left coronary artery from the right ostium with inter arterial course and intramural origin
Left coronary artery from the right ostium with inter arterial course.
Left coronary artery from the right ostium with inter arterial course
RCA from left ostium
RCA from left ostium
RCA from left ostium
RCA from left ostium
RCA from left ostium
Anatomical repair
Anatomical repair
Anatomical repair
Septal course of LAD in the conal septum
Septal course of LAD in the conal septum
Septal course of LAD in the conal septum
Intraseptal left anterior descending coronary artery
Intraseptal left anterior descending coronary artery
Acquired inter arterial course of coronary arteries

CT after arterial switch operation for TGA
Abnormal course
Acquired inter arterial course of coronary arteries

CT after arterial switch operation for TGA
Intramural left main CA
CT after arterial switch operation for TGA
Retroaortic course LMCA
Acquired inter arterial course of coronary arteries

Compression of CA by a stent
Acquired inter arterial course of coronary arteries
Acquired inter arterial course of coronary arteries

Fig. 1
A 28 year old male athlete with a malignant course of the RCA between the aorta and the pulmonary trunk with slight narrowing of the RCA origin on 3D-MRCA (a) and MDCTA (b). Bridging (intramuscular course) of the mid-LAD on 3D-MRCA (c) and MDCTA (d). The super Bruce tread-mill test and scintigraphy were negative. No X-ray coronary angiography was performed.

Fig. 2
A 21 year old male non-athlete with a high ventral aorta origin RCA on 3D-MRCA (a: axial image, b: coronal oblique image) and confirmed on MDCTA (c). The standard Bruce tread-mill test was negative. No scintigraphy or X-ray coronary angiography was performed.

Fig. 3
A 46 year old male athlete with left sinus origin and malignant course of the RCA between the aorta and pulmonary trunk on 3D-MRCA (a) and MDCTA (b). An additional significant soft-plaque stenosis of the mid-RCA (70% lumen narrowing) on MDCTA (c) was missed on 3D-MRCA due to limited coverage. The Agatston coronary calcium score was negative. The super Bruce treadmill test was positive. No scintigraphy was performed. An X-ray coronary angiogram showed an 80% lumen stenosis of the mid-RCA (d). Percutaneous coronary intervention of mid-RCA with bare metal stent implantation was performed (e).

Fig. 4
A 35 year old male athlete with a ventral rotation of RCA originating from the right coronary sinus without malignant course but with possible stenosis on 3D-MRCA (a). The ventral rotation origin of the RCA was confirmed, but no stenosis was seen on MDCTA (b). The super Bruce treadmill test was negative. No scintigraphy or X-ray coronary angiography was performed.


Left Main Coronary Artery Compression During Primary Pulmonary Hypertension

Jean-Frédéric Patrat, Guillaume Jondeau, Olivier Dubourg, Pascal Lacombe, Michel Rigaud, Jean-Pierre Bourdarias and Iraj Gandjbakhch

Chest 1997;112;842-843
Abnormal origin of coronary arteries
Abnormal origin from the aorta

High take off left coronary artery
Abnormal origin from the aorta

High take off left coronary artery
Abnormal origin from the aorta
High take-off of right coronary artery
Abnormal origin from the pulmonary artery: ALCAPA
Abnormal origin from the pulmonary artery: ALCAPA
Abnormal origin from the pulmonary artery: ALCAPA
Abnormal origin from the pulmonary artery: ALCAPA
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Abnormal origin from the pulmonary artery: ARCAPA
Abnormal origin from the pulmonary artery: ARCAPA
Abnormal origin from the pulmonary artery: ARCAPA
Abnormal origin from the pulmonary artery: ARCAPA
Coronary artery from the left ventricle
Abnormal origin from the pulmonary artery: ALCAPA surgery
Abnormal origin from the pulmonary artery: ALCAPA
Mitral regurgitation
Coronary fistulae
Coronary fistulae
Coronary fistulae
Coronary fistulae
Coronary fistulae
Coronary fistulae
Coronary fistulae

Pre-embolization

Post-embolization
Coronary fistulae in PA-IVS & HLHS
Rares anomalies
Hypercholesterolemia
Acquired coronary anomalies

Kawasaki disease
Post-operative coronary obstructions
1. Kawasaki disease (KD) is an acute, self-limited febrile illness of unknown cause that predominantly affects children <5 years of age.

2. KD is now the most common cause of acquired heart disease in children in developed countries.

3. In the absence of pathognomonic tests, the diagnosis continues to rest on the identification of principal clinical findings and the exclusion of other clinically similar entities with known causes.
1. Timely initiation of treatment with intravenous immunoglobulin (IVIG) has reduced the incidence of coronary artery aneurysms defined from absolute luminal dimensions from 25% to \( \approx 4\% \). Ongoing studies with additional therapies have not substantially reduced this residual risk.

2. The long-term prognosis is determined by the initial and current level of coronary artery involvement. Certain subsets of patients are at risk for myocardial ischemia from coronary artery thrombosis and stenoses.

3. Medical management of such patients hinges on judicious use of thromboprophylaxis and vigilance to identify evolving stenoses. Invasive revascularization procedures might be required for selected patients.
Natural history of coronary artery abnormalities
Epicardial coronary artery (right) and epicardial vein (left) from a 19-month-old child who died 10 months after Kawasaki disease onset.

Luminal myofibroblastic proliferation
Thrombosis of giant coronary artery aneurysms in Kawasaki disease
Clinical criteria for the diagnosis of Kawasaki disease

Classic KD is diagnosed in the presence of **fever for at least 5 days** (the day of fever onset is taken to be the first day of fever) together with **at least 4 of the 5** following principal clinical features:

1. Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
2. Bilateral bulbar conjunctival injection without exudate
3. Rash: maculopapular, diffuse erythroderma, or erythema multiforme-like
4. Erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase
5. Cervical lymphadenopathy (≥1.5 cm diameter), usually unilateral
Clinical features of classic Kawasaki disease.
Clinical features of classic Kawasaki disease.
Clinical features of classic Kawasaki disease.
Clinical features of classic Kawasaki disease.
Clinical features of classic Kawasaki disease.
Evaluation of suspected incomplete Kawasaki disease

Children with fever $\geq 5$ days and 2 or 3 compatible clinical criteria OR
Infants with fever for $\geq 7$ days without other explanation

Assess Laboratory Tests

CRP$<$3.0 mg/dL and ESR$<$40 mm/hr

- Serial clinical and laboratory re-evaluation if fevers persist
  - Echocardiogram if typical peeling develops

CRP$\geq$3.0 mg/dL and/or ESR$\geq$40 mm/hr

- 3 or more Laboratory Findings:
  1) Anemia for age
  2) Platelet count of $\geq 450,000$ after the 7th day of fever
  3) Albumin $\leq 3.0$ g/dL
  4) Elevated ALT level
  5) WBC count of $\geq 15,000$/mm$^3$
  6) Urine $\geq 10$ WBC/hpf

Treat

OR

Positive echocardiogram
Kawasaki disease, coronary dilatation & aneurysms
Z-Score Classification in Kawasaki disease

1. No involvement: Always <2
2. Dilation only: 2 to <2.5; or if initially <2, a decrease in Z score during follow-up ≥ 1
3. Small aneurysm: ≥ 2.5 to <5
4. Medium aneurysm: ≥ 5 to <10, and absolute dimension <8 mm
5. Large or giant aneurysm: ≥ 10, or absolute dimension ≥ 8 mm
Mean and prediction limits for 2 and 3 SDs for size of (A) LAD, (B) proximal RCA, and (C) LMCA according to body

Recommendations for Cardiovascular Assessment for Diagnosis and Monitoring During the Acute Illness

1. **Echocardiography** should be performed when the diagnosis of KD is considered, but unavailability or technical limitations should not delay treatment.

2. Coronary arteries should be imaged, and **quantitative assessment of luminal dimensions**, normalized as Z scores adjusted for body surface, should be performed.

3. For **uncomplicated patients**, echocardiography should be repeated both within 1 to 2 weeks and 4 to 6 weeks after treatment.

4. For **patients with important and evolving coronary artery abnormalities** (Z score > 2.5) detected during the acute illness, more frequent echocardiography (at least twice per week) should be performed until luminal dimensions have stopped progressing to determine the risk for and presence of thrombosis.

5. To detect coronary artery thrombosis, it may be reasonable to perform echocardiography for **patients with expanding large or giant aneurysms twice per week while dimensions are expanding rapidly and at least once weekly in the first 45 days of illness, and then monthly until the third month after illness onset**, because the failure to escalate thromboprophylaxis in time with the rapid expansion of aneurysms is a primary cause of morbidity and mortality.
Recommendations for Initial Treatment
With IVIG and ASA

1. Patients with complete KD criteria and those who meet the algorithm criteria for incomplete KD should be treated with high-dose IVIG (2 g/kg given as a single intravenous infusion) within 10 days of illness onset but as soon as possible after diagnosis.

2. It is reasonable to administer IVIG to children presenting after the 10th day of illness (ie, in whom the diagnosis was missed earlier) if they have either persistent fever without other explanation or coronary artery abnormalities together with ongoing systemic inflammation, as manifested by elevation of ESR or CRP (CRP > 3.0 mg/dL).

3. Administration of moderate- (30–50 mg/kg/d) to high-dose (80–100 mg/kg/d) ASA is reasonable until the patient is afebrile, although there is no evidence that it reduces coronary artery aneurysms.

4. IVIG generally should not be administered to patients beyond the tenth day of illness in the absence of fever, significant elevation of inflammatory markers, or coronary artery abnormalities.

5. The ESR is accelerated by IVIG therapy and therefore should not be used to assess response to IVIG therapy. A persistently high ESR alone should not be interpreted as a sign of IVIG resistance.
Recommendations for Adjunctive Therapies for Primary Treatment

1. Single-dose pulse methylprednisolone should not be administered with IVIG as routine primary therapy for patients with KD.

2. Administration of a longer course of corticosteroids (eg, tapering over 2–3 weeks), together with IVIG 2 g/kg and ASA, may be considered for treatment of high-risk patients with acute KD, when such high risk can be identified in patients before initiation of treatment.
Recommendations for Adjunctive Therapies for Primary Treatment

1. It is reasonable to administer a second dose of IVIG (2 g/kg) to patients with persistent or recrudescent fever at least 36 hours after the end of the first IVIG infusion.

2. Administration of high-dose pulse steroids usually methylprednisolone 20–30 mg/kg intravenously for 3 days, with or without a subsequent course and taper of oral prednisone) may be considered as an alternative to a second infusion of IVIG or for retreatment of patients with KD who have had recurrent or recrudescent fever after additional IVIG.

3. Administration of a longer (eg, 2–3 weeks) tapering course of prednisolone or prednisone, together with IVIG 2 g/kg and ASA, may be considered in the retreatment of patients with KD who have had recurrent or recrudescent fever after initial IVIG treatment.

4. Administration of infliximab (5 mg/kg) may be considered as an alternative to a second infusion of IVIG or corticosteroids for IVIG-resistant patients.

5. Administration of cyclosporine may be considered in patients with refractory KD in whom a second IVIG infusion, infliximab, or a course of steroids has failed.

6. Administration of immunomodulatory monoclonal antibody therapy (except TNF-α blockers), cytotoxic agents, or (rarely) plasma exchange may be considered in highly refractory patients who have failed to respond to a second infusion of IVIG, an extended course of steroids, or infliximab.
Recommendations for Prevention of Thrombosis During the Acute Illness

1. **Low-dose ASA** (3–5 mg/kg/d) should be administered to patients without evidence of coronary artery changes until 4 to 6 weeks after onset of illness.

2. For patients with **rapidly expanding coronary artery aneurysms or a maximum Z score of ≥ 10**, **systemic anticoagulation** with LMWH or warfarin (international normalized ratio target 2.0–3.0) in addition to low-dose ASA is reasonable.

3. For patients at increased risk of thrombosis, for example, with large or giant aneurysms (≥ 8 mm or Z score ≥ 10) and a recent history of coronary artery thrombosis, “triple therapy” with ASA, a second antiplatelet agent, and anticoagulation with warfarin or LMWH may be considered.

4. Ibuprofen and other nonsteroidal antiinflammatory drugs with known or potential involvement of cyclooxygenase pathway may be harmful in patients taking ASA for its antiplatelet effects.
Acquired coronary anomalies

Kawasaki disease

Post-operative coronary obstructions
Aims of coronary artery evaluation in TGA

• Before arterial switch operation
  – No interest (except for the choice of the surgeon)

• CA status after arterial switch operation
  – Early postoperative control after CA transfer
    • In cases of difficult transfer: intramural course
    • Post-operative myocardial ischemia
  – Midterm control
    • Prevalence of CA obstruction = 5 to 7% 
      (Legendre et al. Circulation 2003;108 suppl1:II186-90)
    • Can be found in asymptomatic children
Coronary artery distribution and mortality after ASO
Pasquali, 2002

Type B

• Single ostium and intramural course increase the risk of postoperative death
• Postoperative mortality is increased in patients with abnormal coronary artery distribution (OR 1,7).

Intramural course
Late coronary artery anomalies after ASO

• Minor distortion during transfer ? : endothelium, intimal proliferation, ...

• Evolution : compression, stretching

• Outcome
  – Sudden death and myocardial infarction
    • Before 6 months of age
  – Asymptomatic myocardial ischemia
    • Balance between intimal proliferation and development of collateral circulation
  – Coronary occlusion without ischemia
Indications to control CA after ASO

• Any time in case of patent myocardial ischemia
• Systematic screening in school age children
• What has to be detected?
  – CA obstruction : imaging
    • Prevalence vs risk of diagnostic procedure
  – Myocardial ischemia : function
    • Negative predictive value ? (>50% false negative)
    • Positive predictive value OK (few false positive)
Late coronary artery anomalies after ASO
64-slice CT after arterial switch operation for TGA

Intramural left main CA
64-slice CT after arterial switch operation for TGA
LMCA stenosis
64-slice CT after arterial switch operation for TGA

Abnormal course
64-slice CT after arterial switch operation for TGA
LMCA retro-aortic course
64-slice CT after arterial switch operation for TGA
RCA compression
How to treat CA obstructions?

CA surgical angioplasty

PTCA
Conclusion

• Wide variety of CA anomalies
• Recent advances in non invasive imaging n children
• New insights in the mechanisms of post-ASO coronary obstruction
• Still a surgical challenge in CHD