# Congenital and acquired coronary artery anomalies in children

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Centre de Référence Maladies Rares
Malformations Cardiaques Congénitales Complexes-M3C
Centre de Référence Maladies Rares
**Maladies Cardiaques Héréditaires- CARDIOGEN**
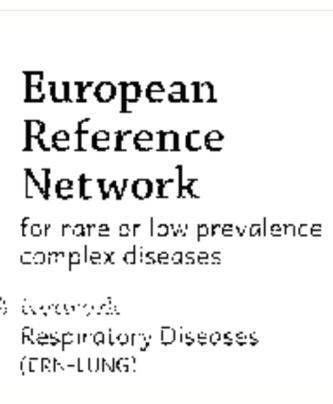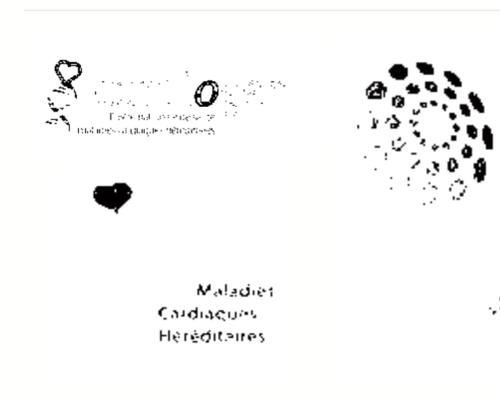
Very short embryology of coronary arteries

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
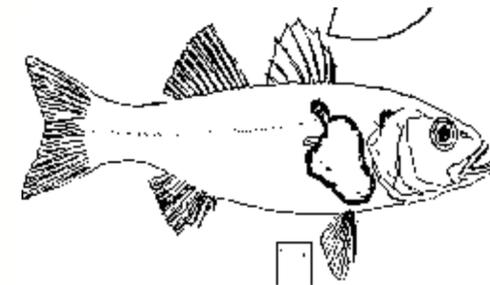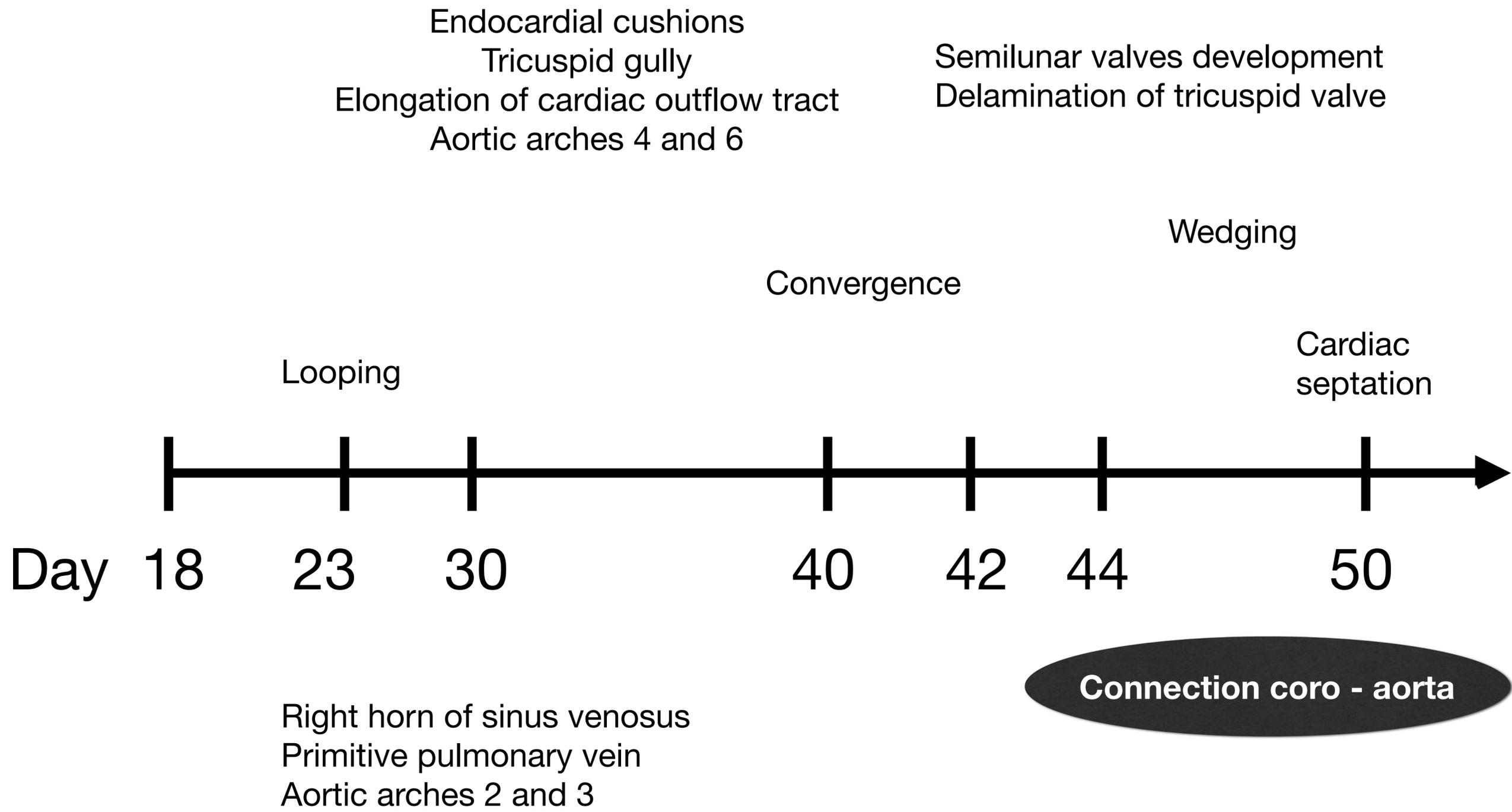
Origin of the coronary vessels : venous pole

- Endothelial cells of the sinus venosus (venous pole) + endocardium
- Dedifferentiation of the venous cells
- Invasion of the myocardium : coronary arteries
- Superficial vessels : veins


K Red-Horse et al. Nature 2010;464, 549-53
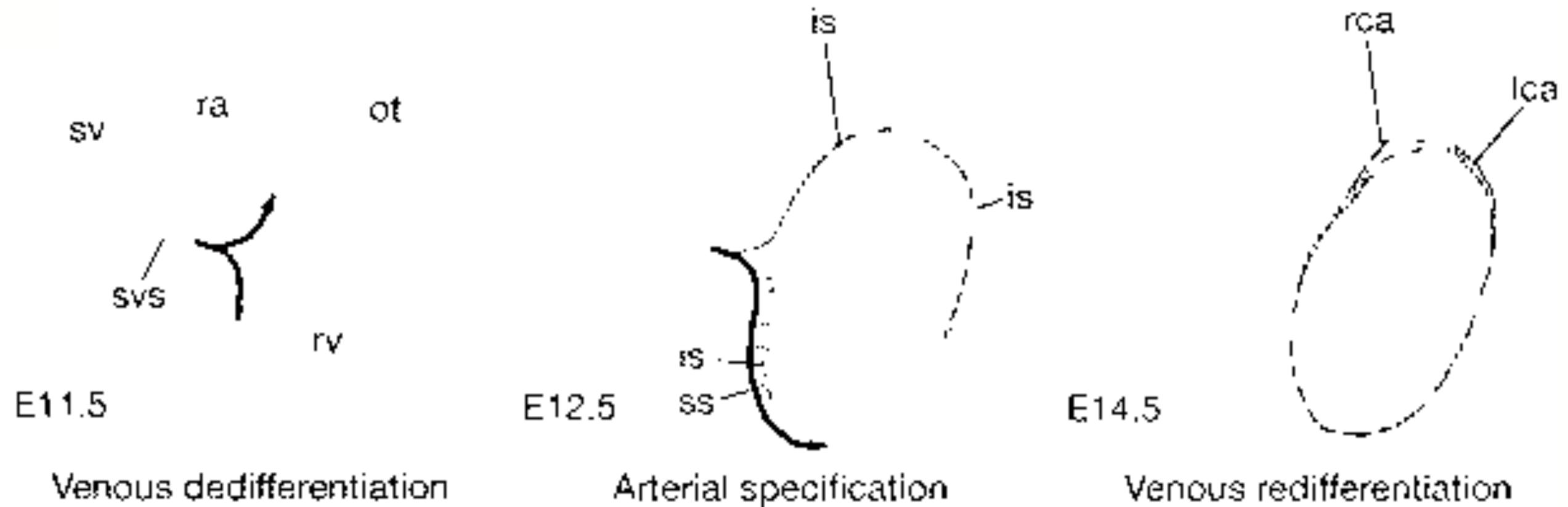
# Embryology : EMT (epithelial-to-mesenchyme transformation)

- migrate within the conjonctive tissue of the subepicardial space.

- Then in newly formed spaces within the developing myocardium (intramyocardial spaces)

- These two spaces are continuous, but no communication with the ventricular lumen

- The endocardium is intact : **no myocardial sinusoids**

Epithelium

Endocardium

Mesenchyme

Intramyocardial spaces
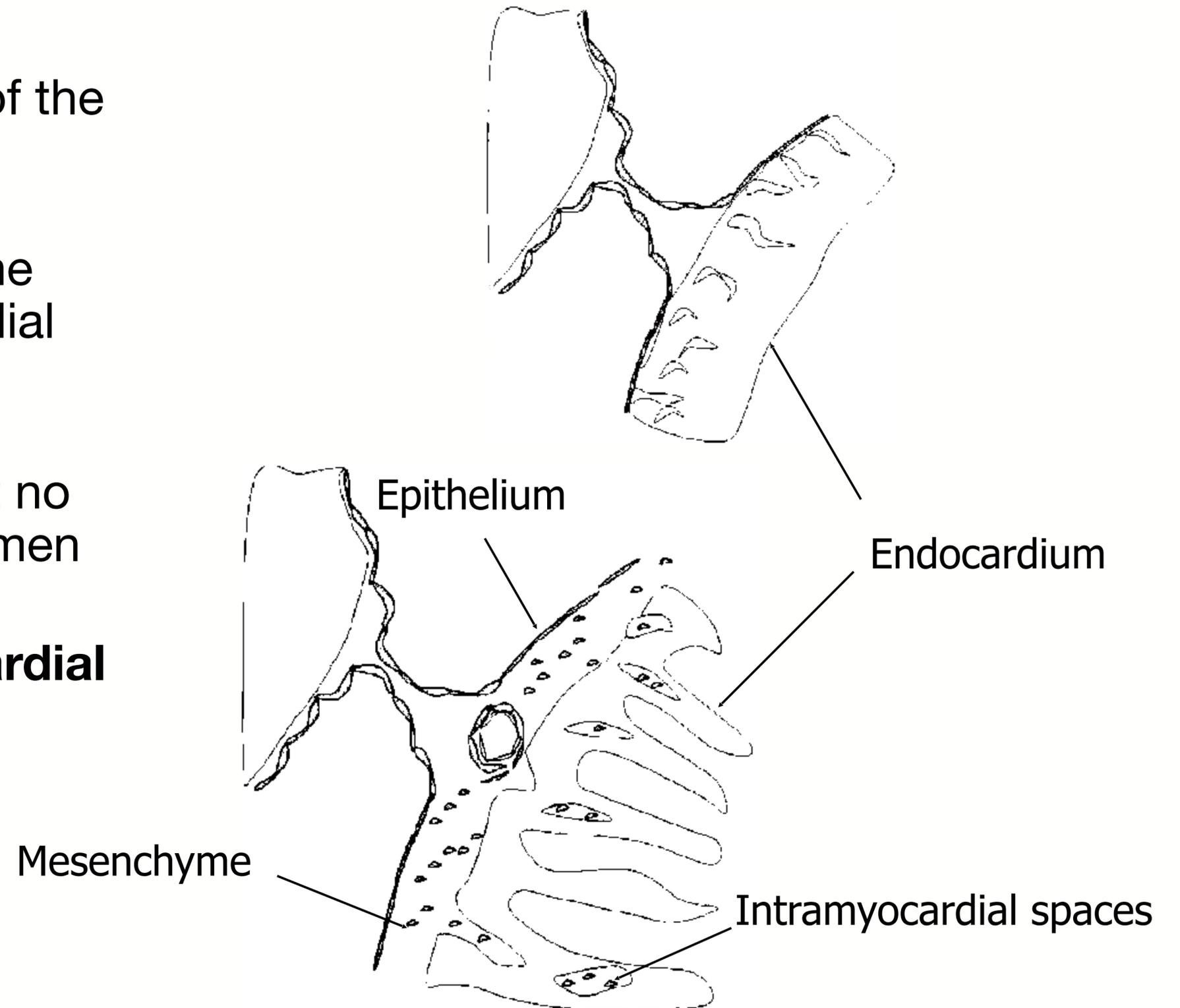
Coronary artery patterning in *Tbx1*^{-/-} hearts

Tbx1^{+/-}
Connexin40
eGFP

LCA
Ao
RCA
PT

96-16
Ao
PT
Tbx1^{+/-}
Tbx1^{-/-}
96-16

Tbx1^{+/+}   *Tbx1*^{-/-}

Théveniau-Ruissy et al Circulation Research 2008;103:142-8
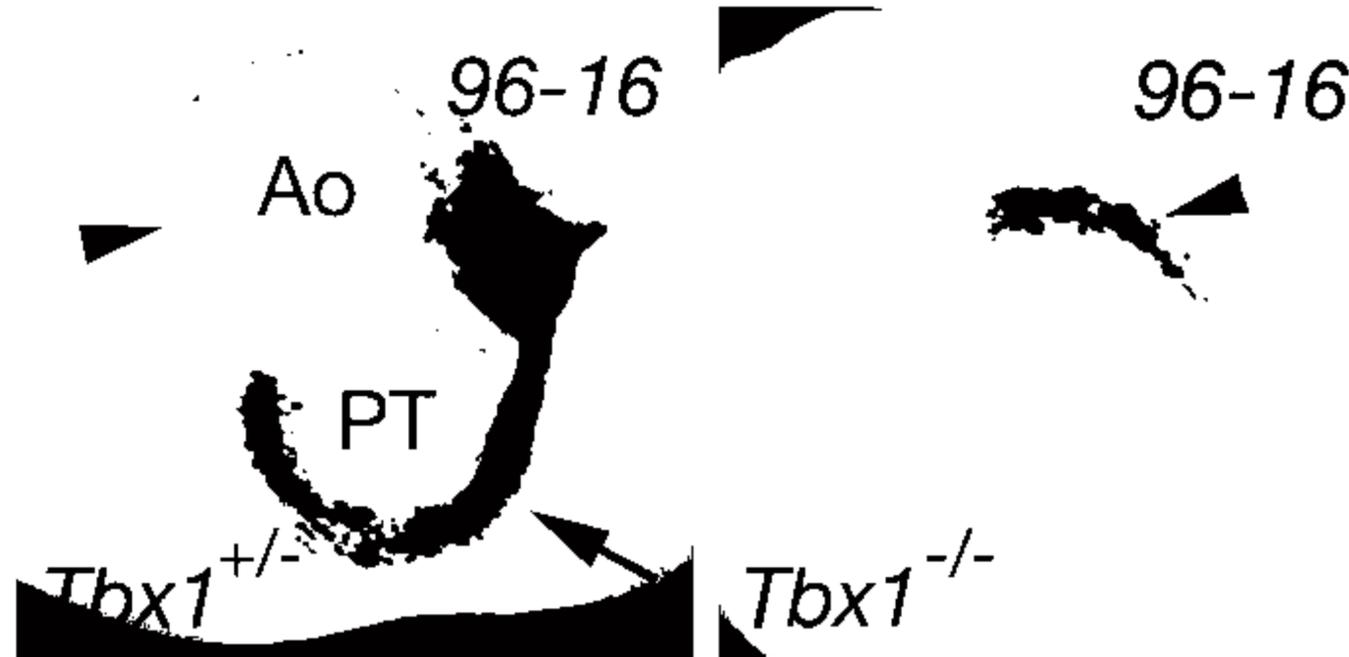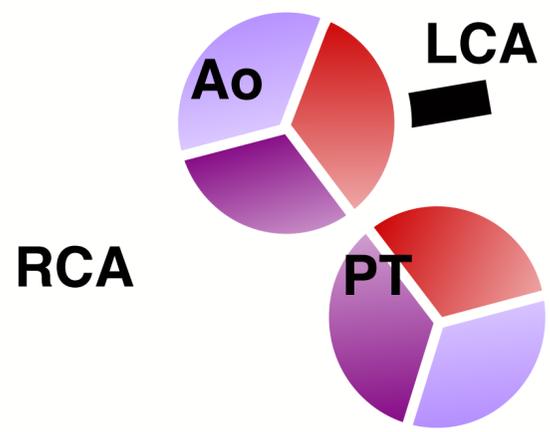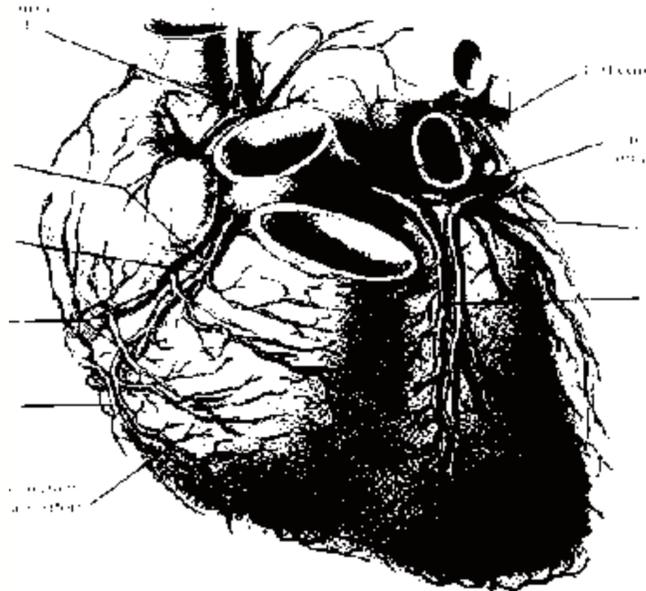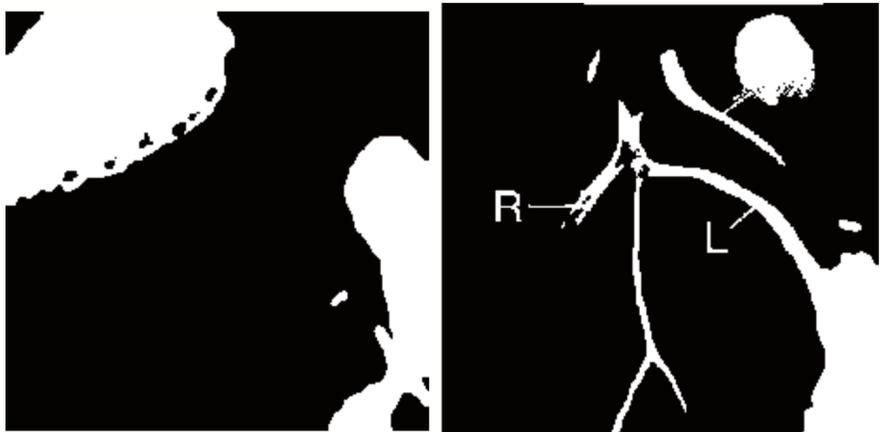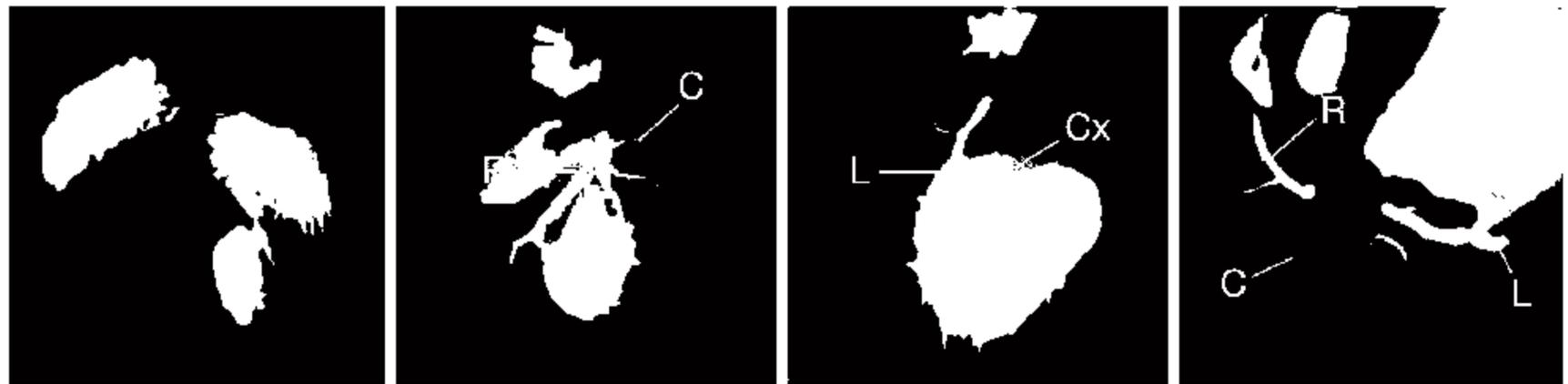
Coronary sinuses are formed via ingrowth of the peritruncal capillary plexus
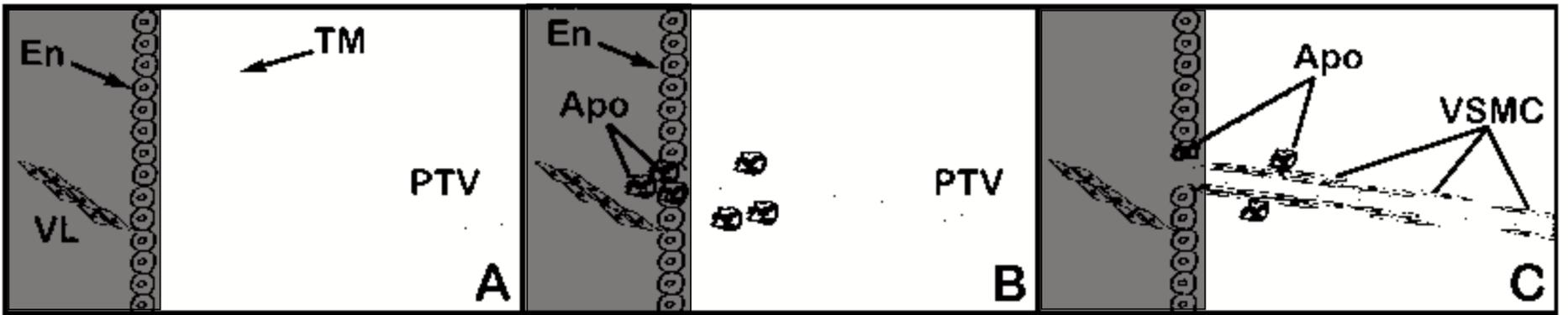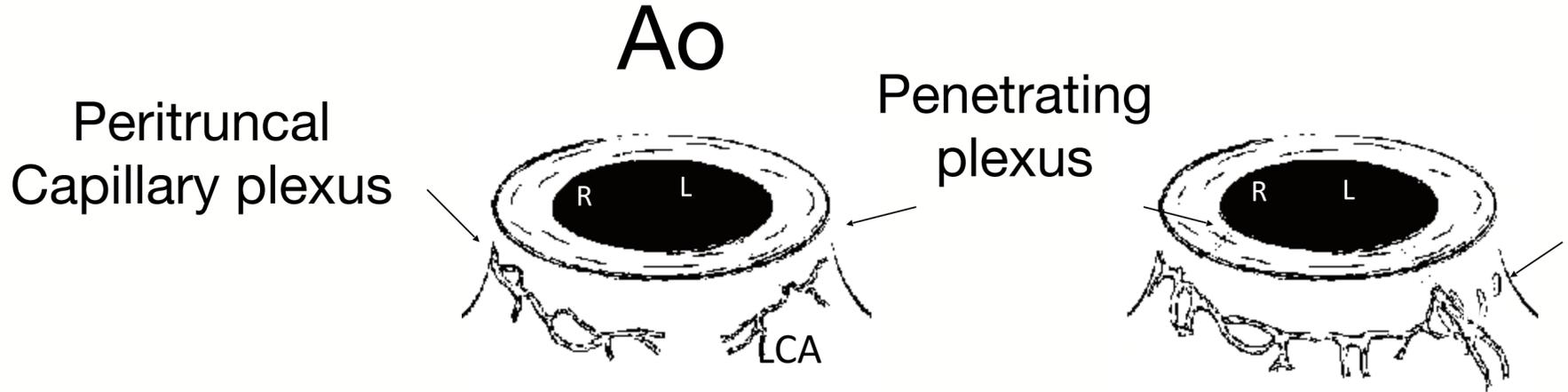
Hypoxia and apoptosis are correlated with the invasion of the Aorta

Tomanek RJ, Angiogenesis, 2005

Coronary artery patterning in *Tbx1-/-* hearts

Ao
LCA
RCA
PT
RCA

Tbx1+/-

LCA

Tbx1-/-

Tbx1+/-
PECAM

Tbx1-/-
PECAM

Théveniau-Ruissy et al Circulation Research 2008;103:142-8
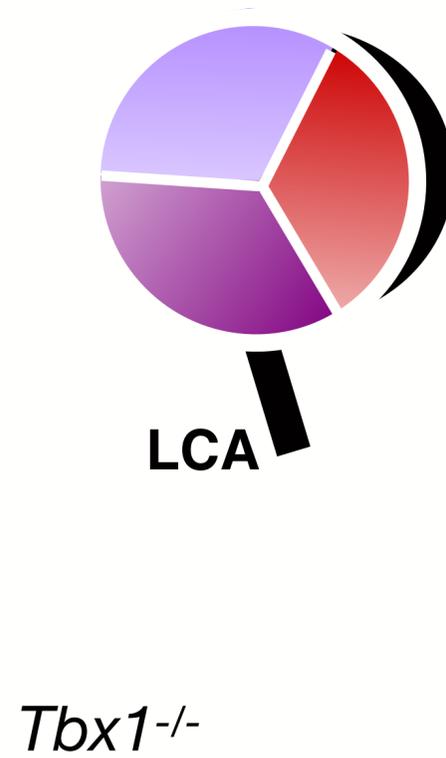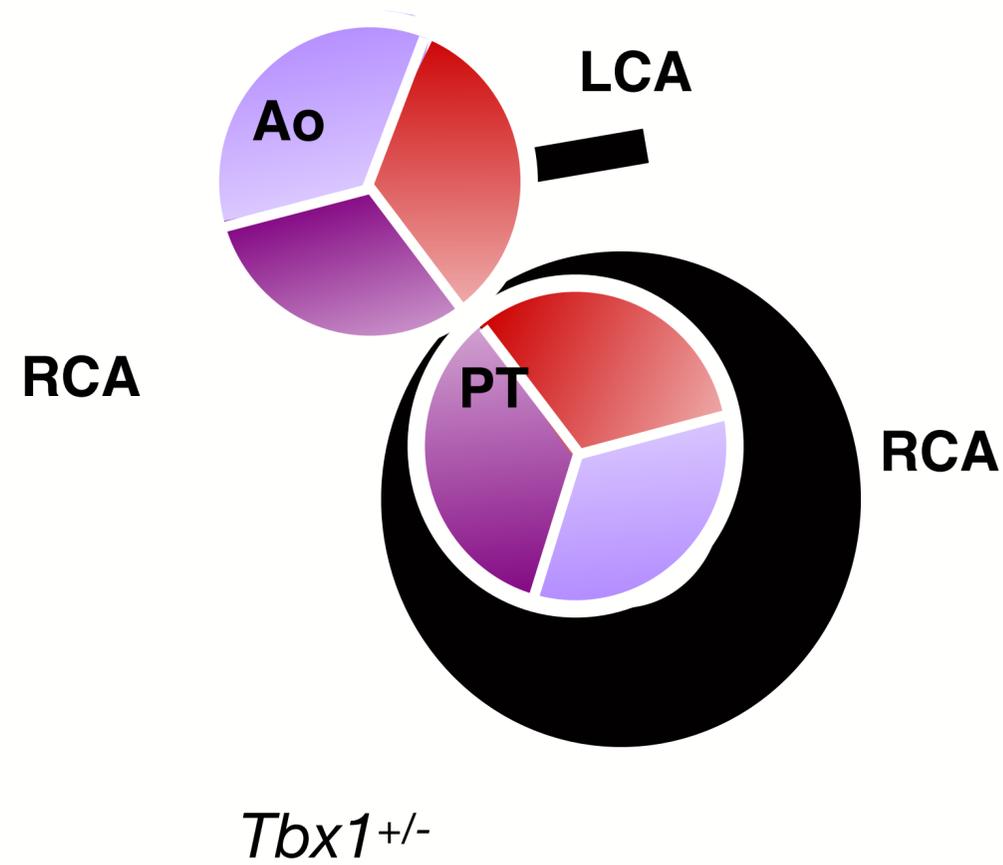
Embryology : the coronary arteries enter the aorta

- 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)
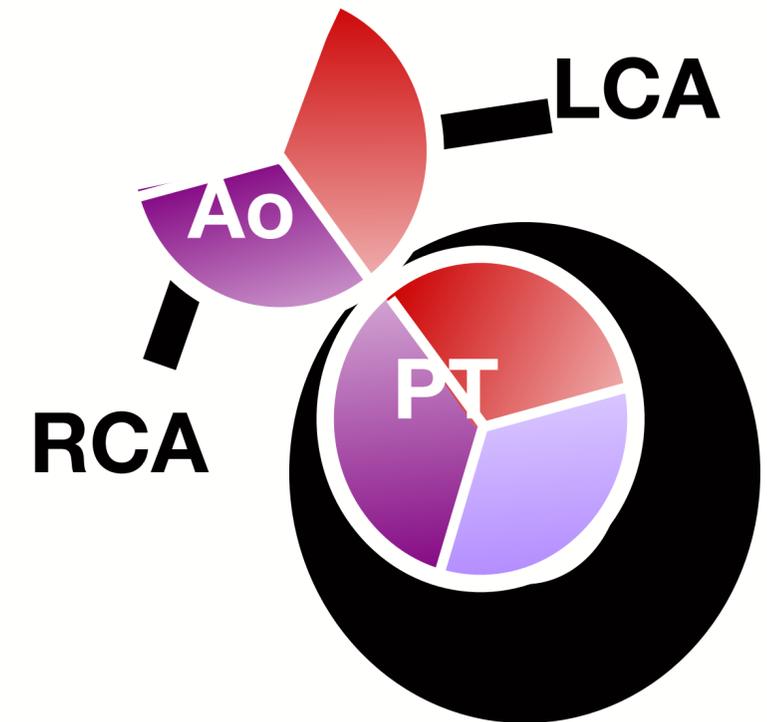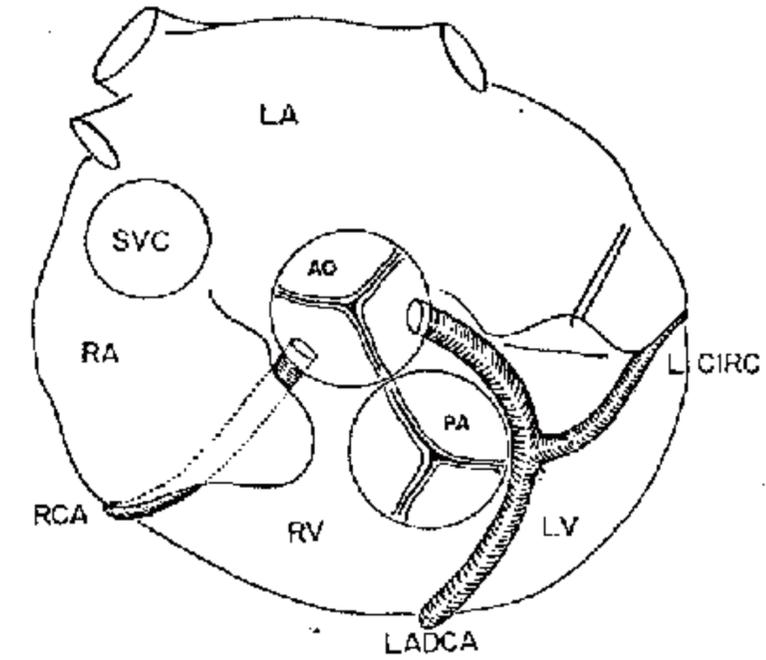
Conotruncal defects

- The location of the coronary ostia depends on the degree of rotation of the outflow tract (which modifies the location of the subpulmonary domain)
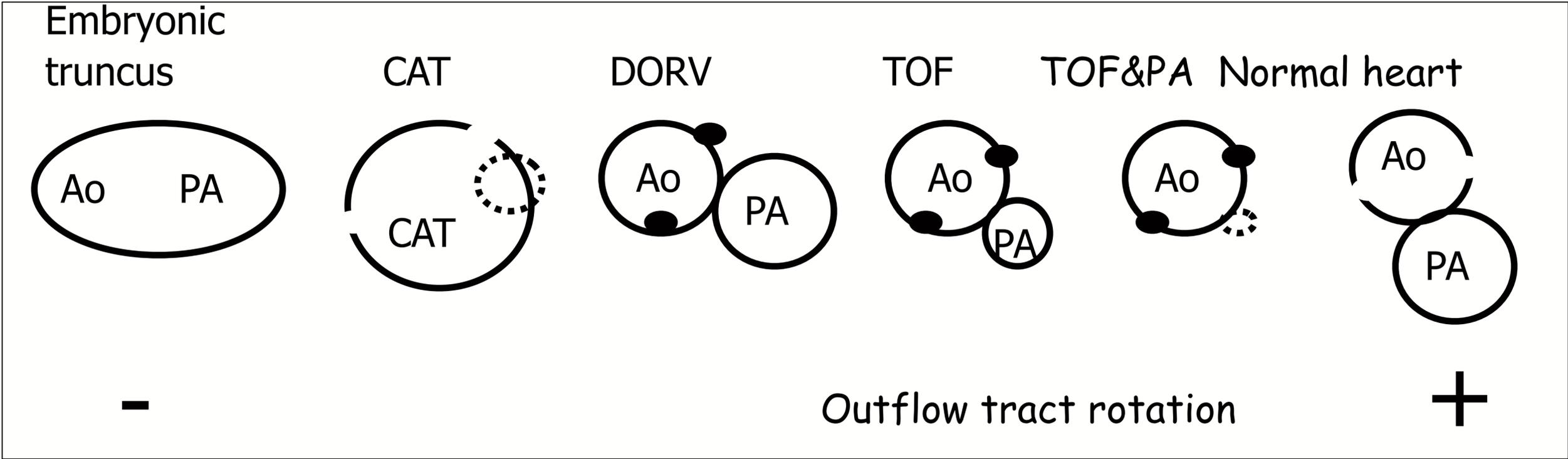
# Detection of myocardial ischemia in children

SPECT Tl-201 effort
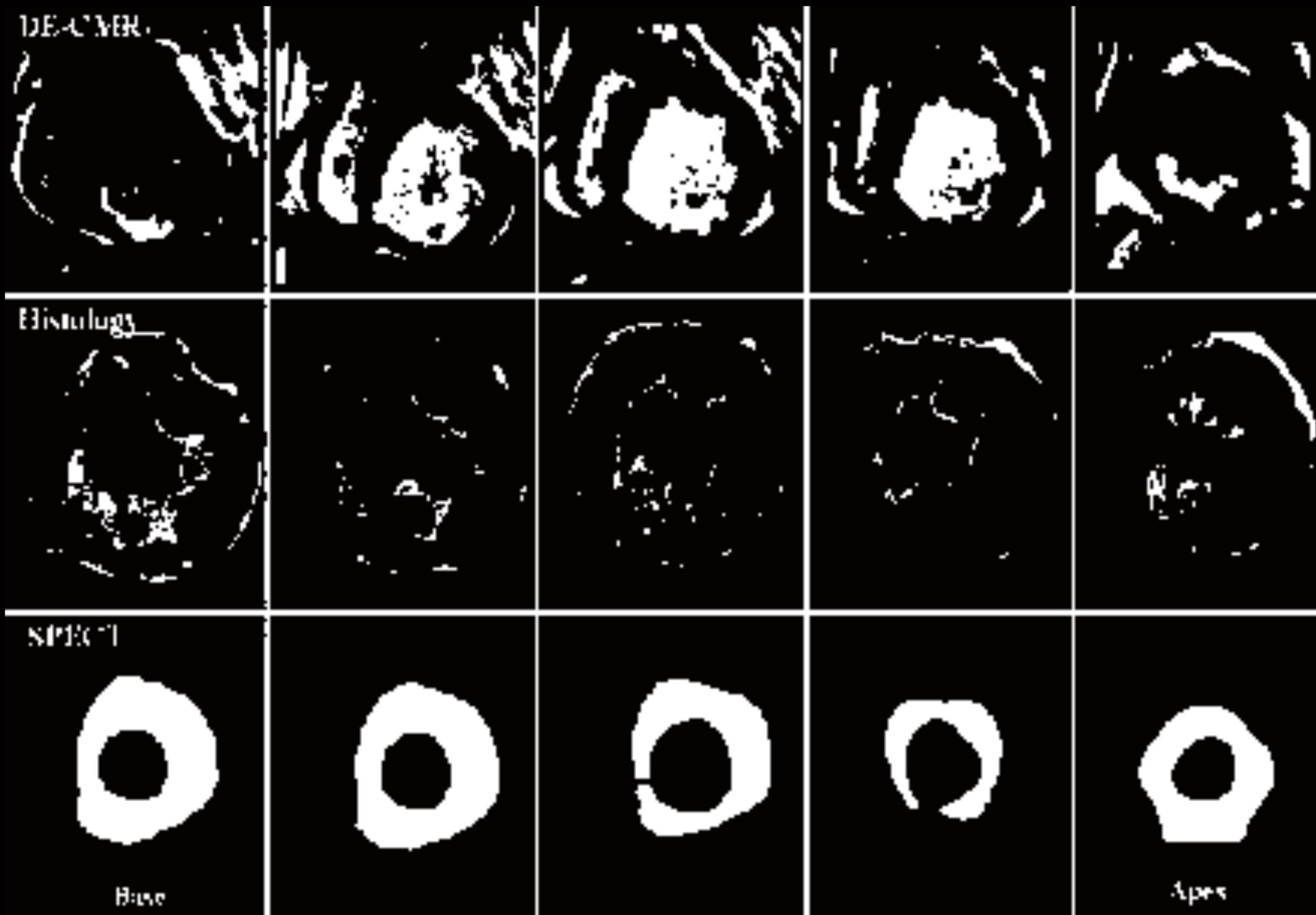
Are congenital coronary anomalies a cause of death in young patients ?

Group (Age)	No. of Deaths	Deaths Related to Coronary Anomalies, %
Exercising individuals, overall (8–66 y)[18]	550	11
General population (<40 y)[17]	162	0.6
Competitive athletes (mean age, 17 y)[19]	134	23
Joggers and marathon runners (30–46 y)[18]	120	1.6
Exercising individuals, Maryland State[18]	62	0

Angelini et al. Circulation 2002

Abnormal epicardial course of coronary arteries & abnormal origin from the aorta

Main abnormal epicardial courses of coronary arteries
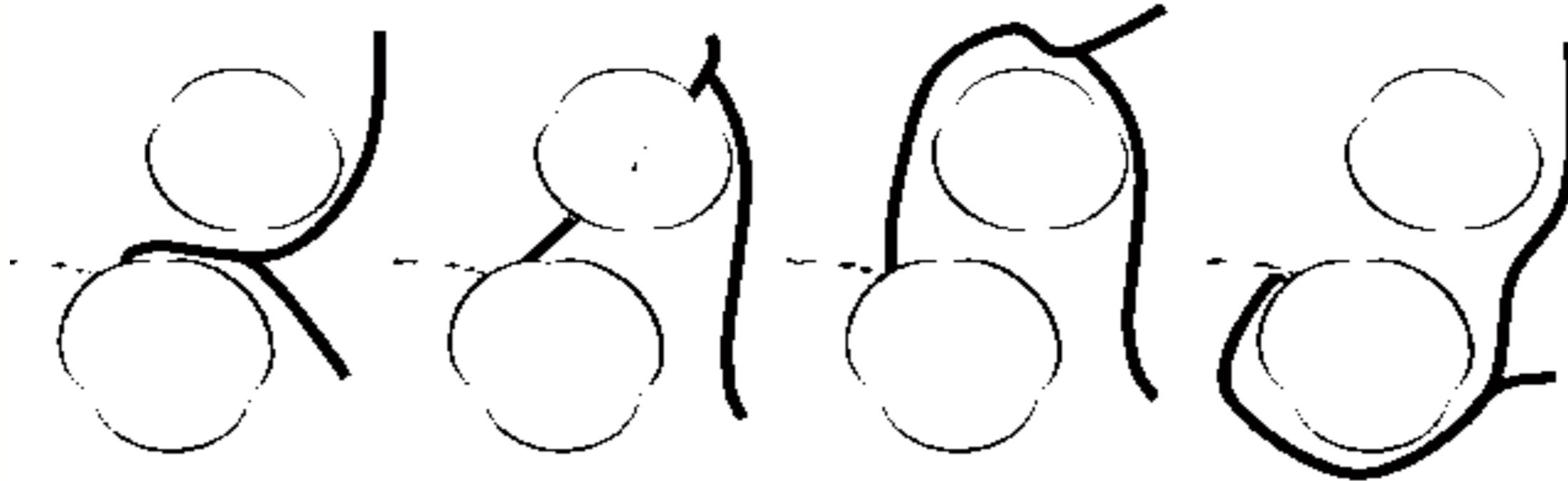

Interarterial Course   Septal Course   Anterior Course   Retroaortic Course
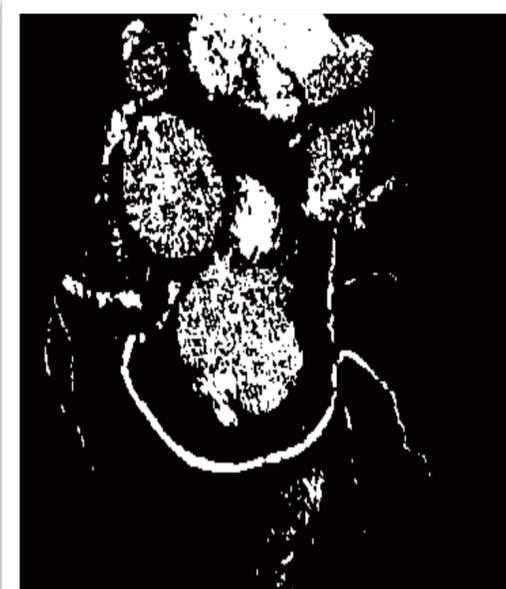
Abnormal courses considered at low risk of cardiac event
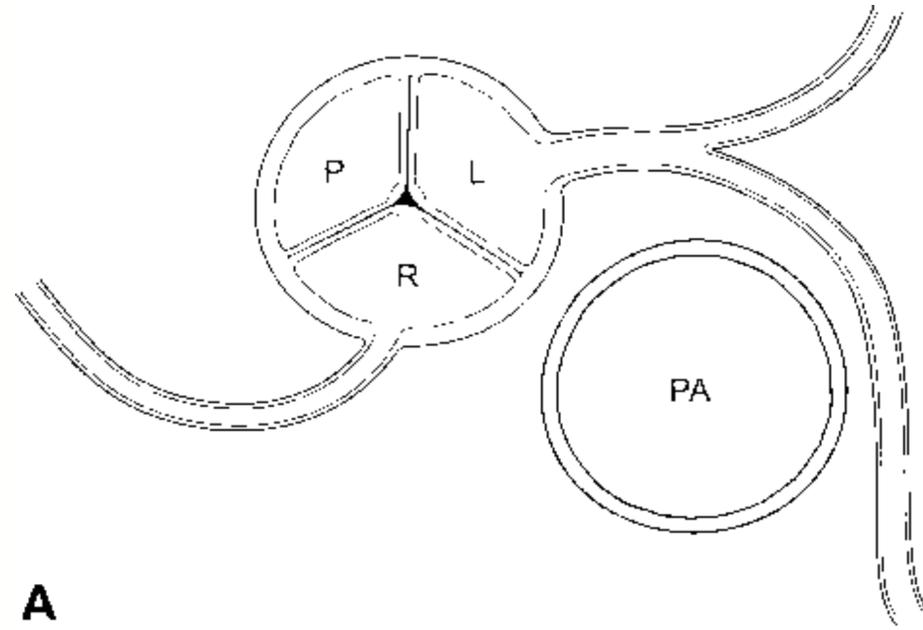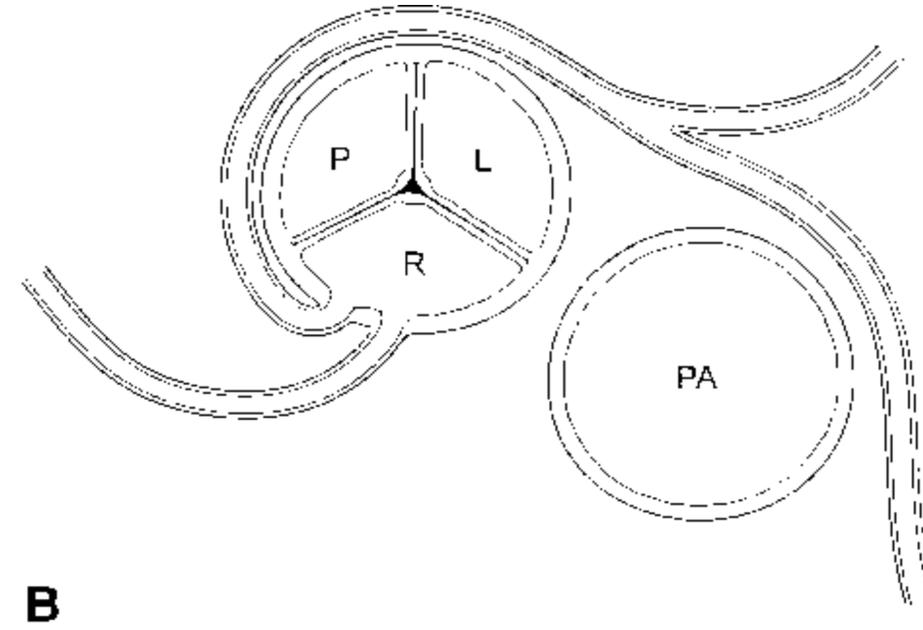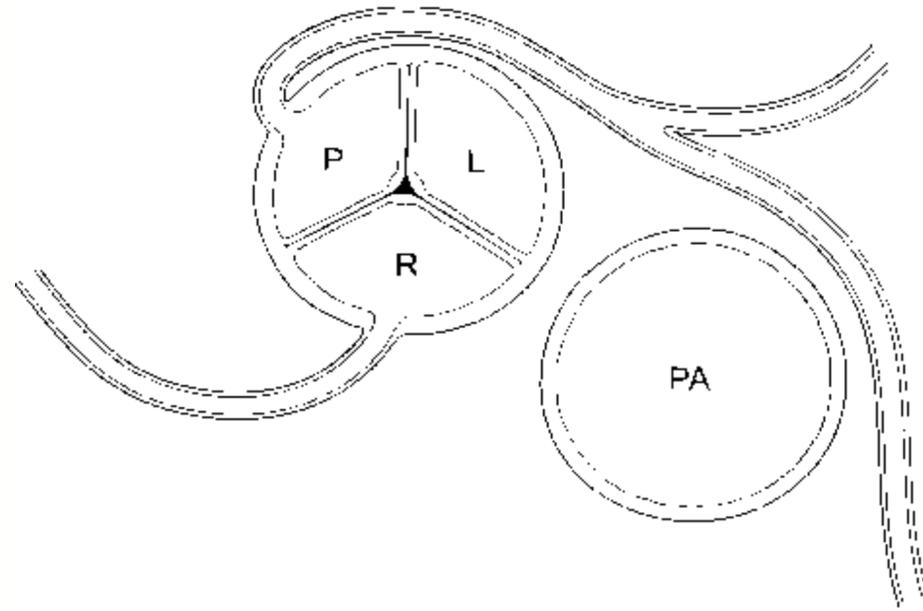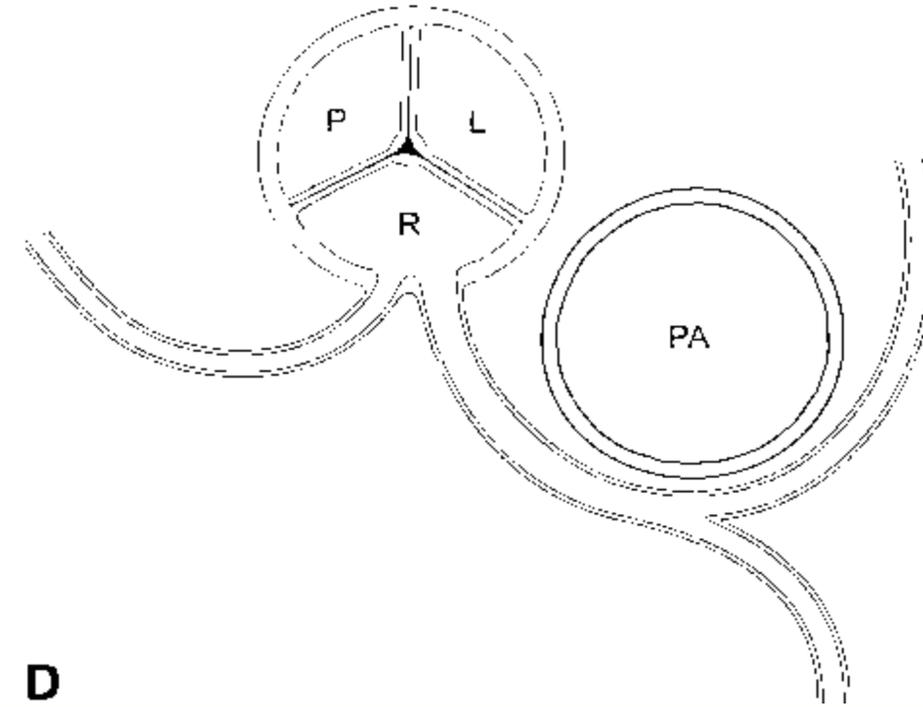
Abnormal courses considered of cardiac event
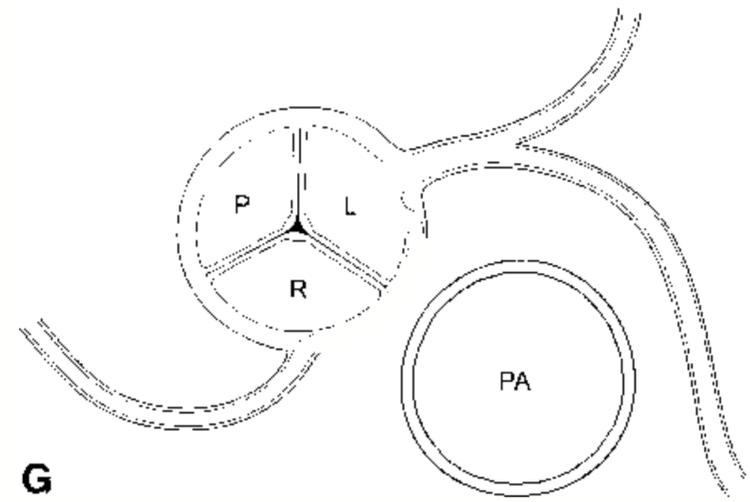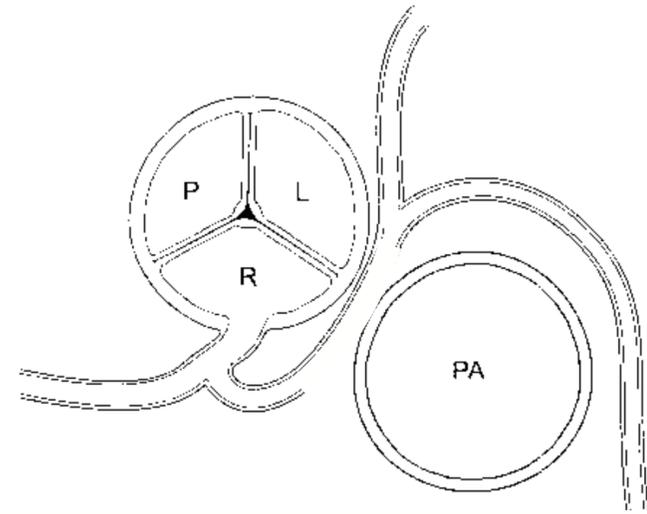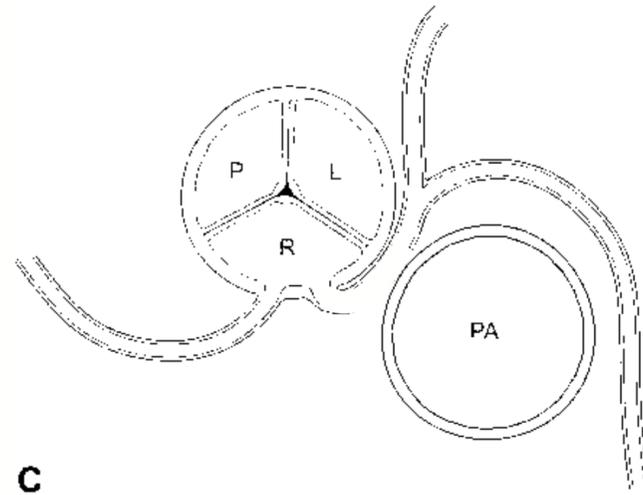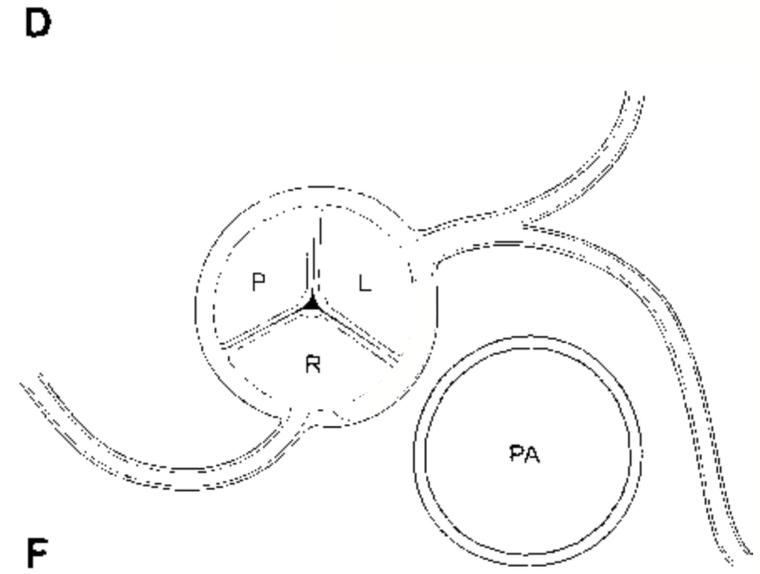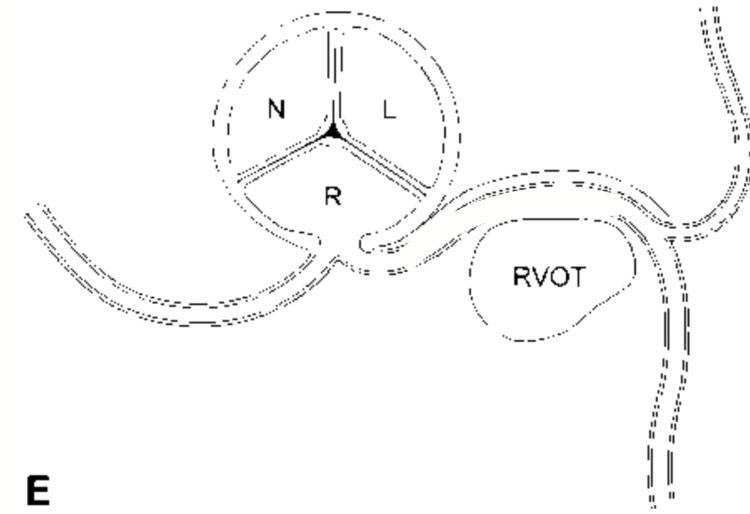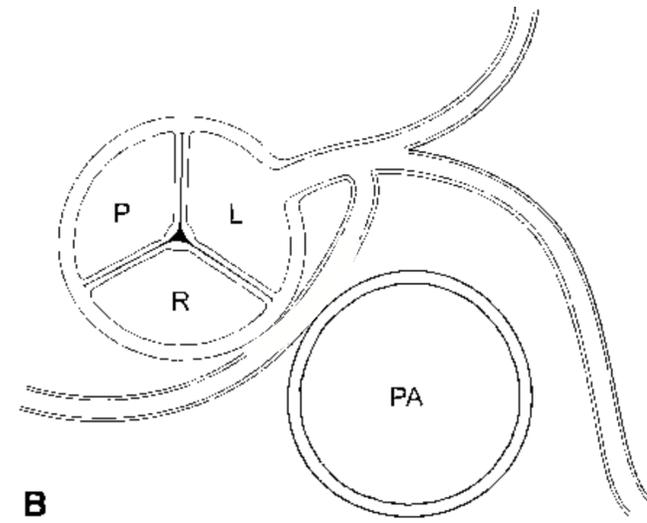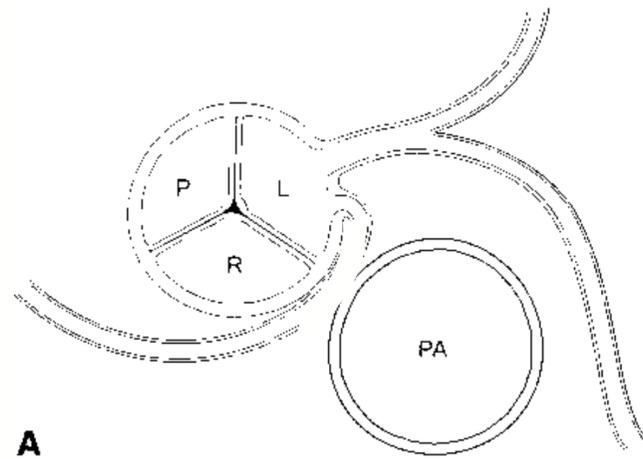
Main abnormal epicardial courses
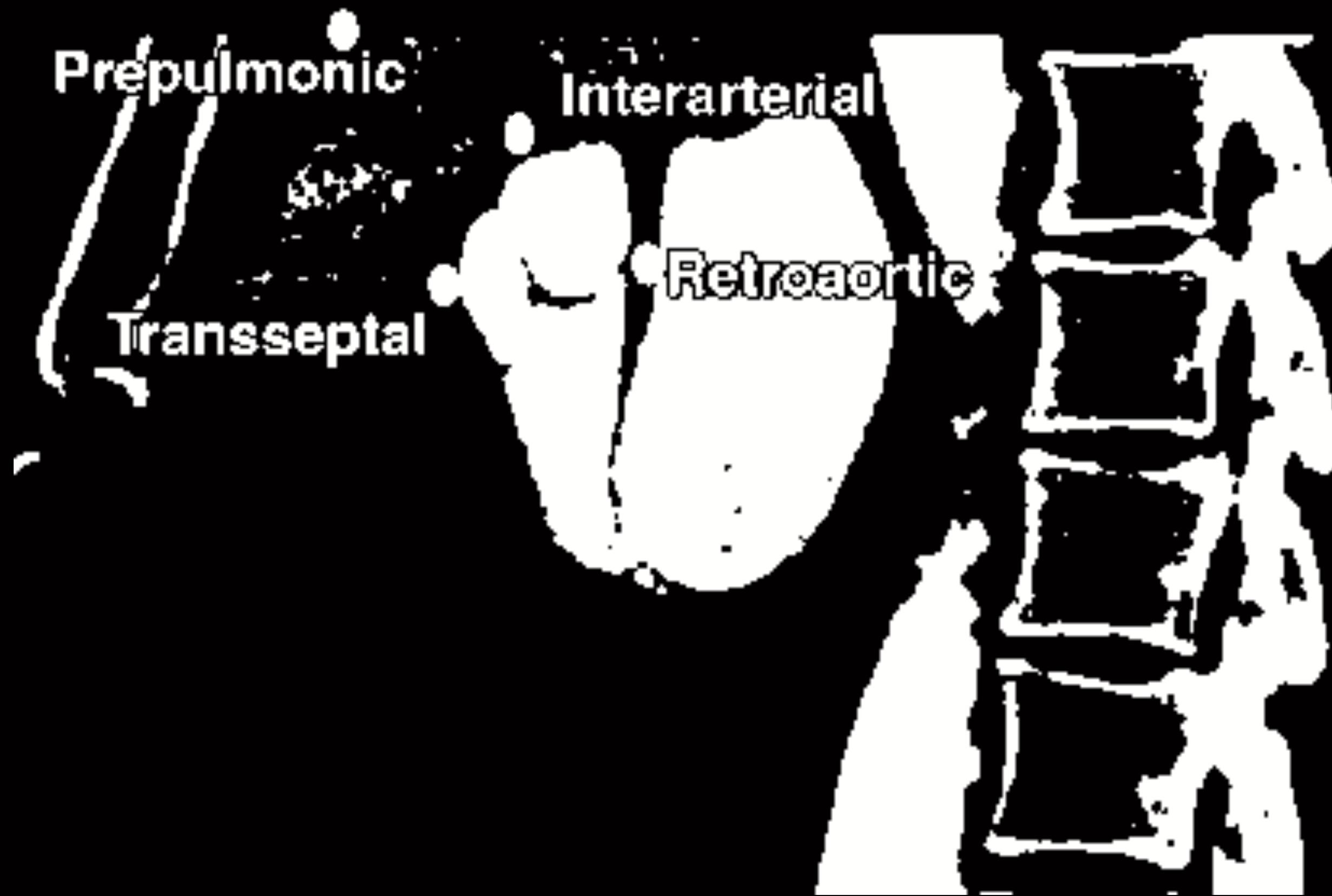
Mechanism of myocardial ischemia
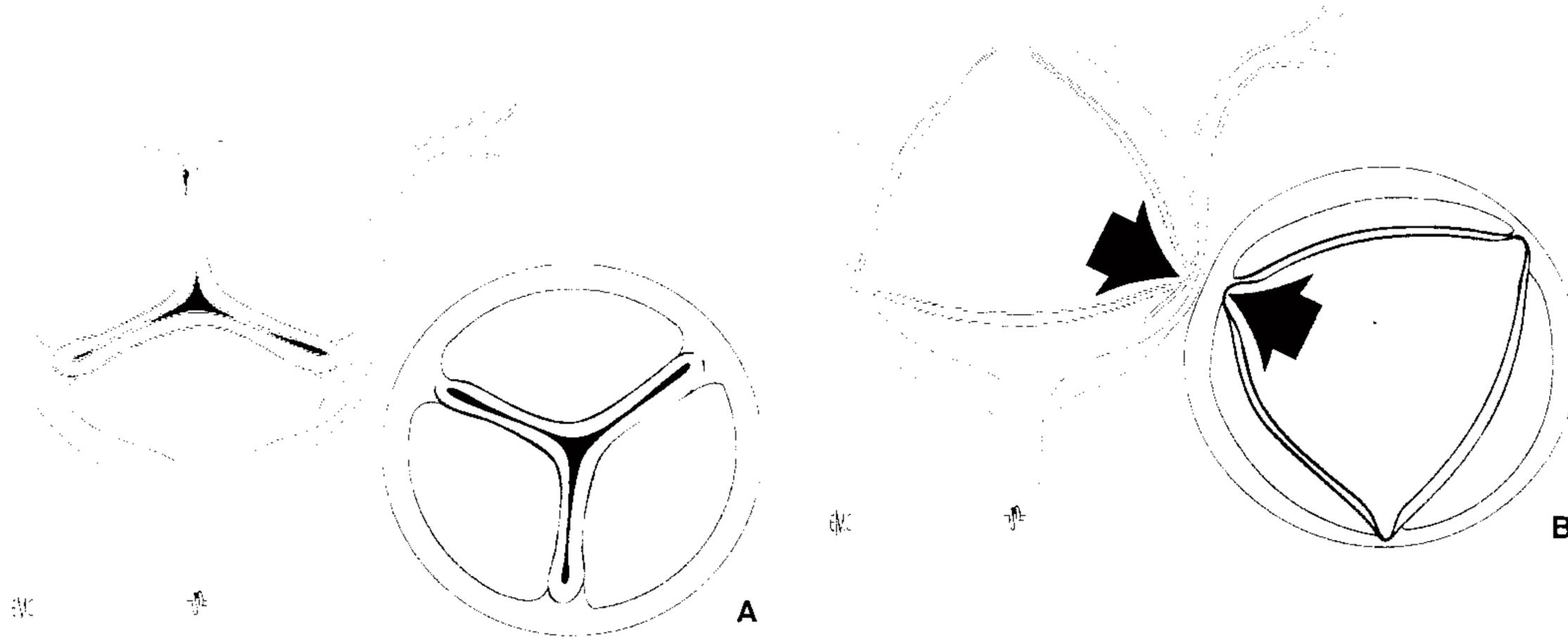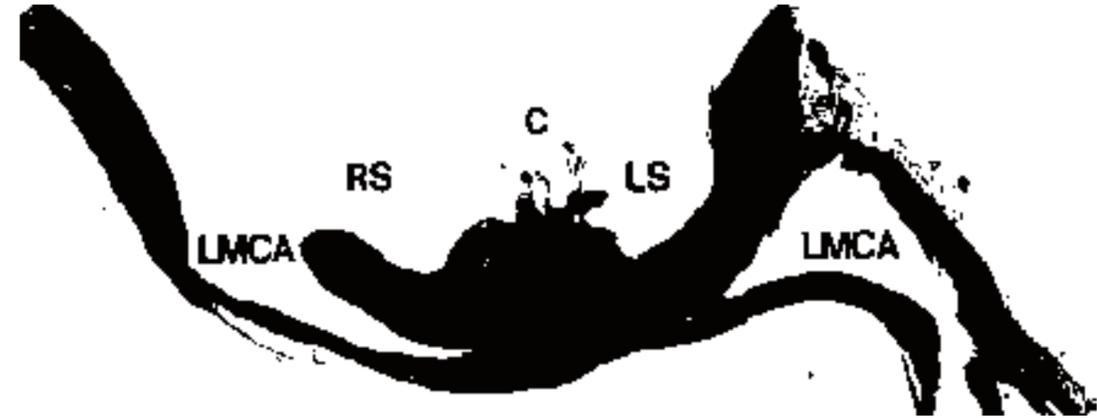
Serendipitously diagnosed or not
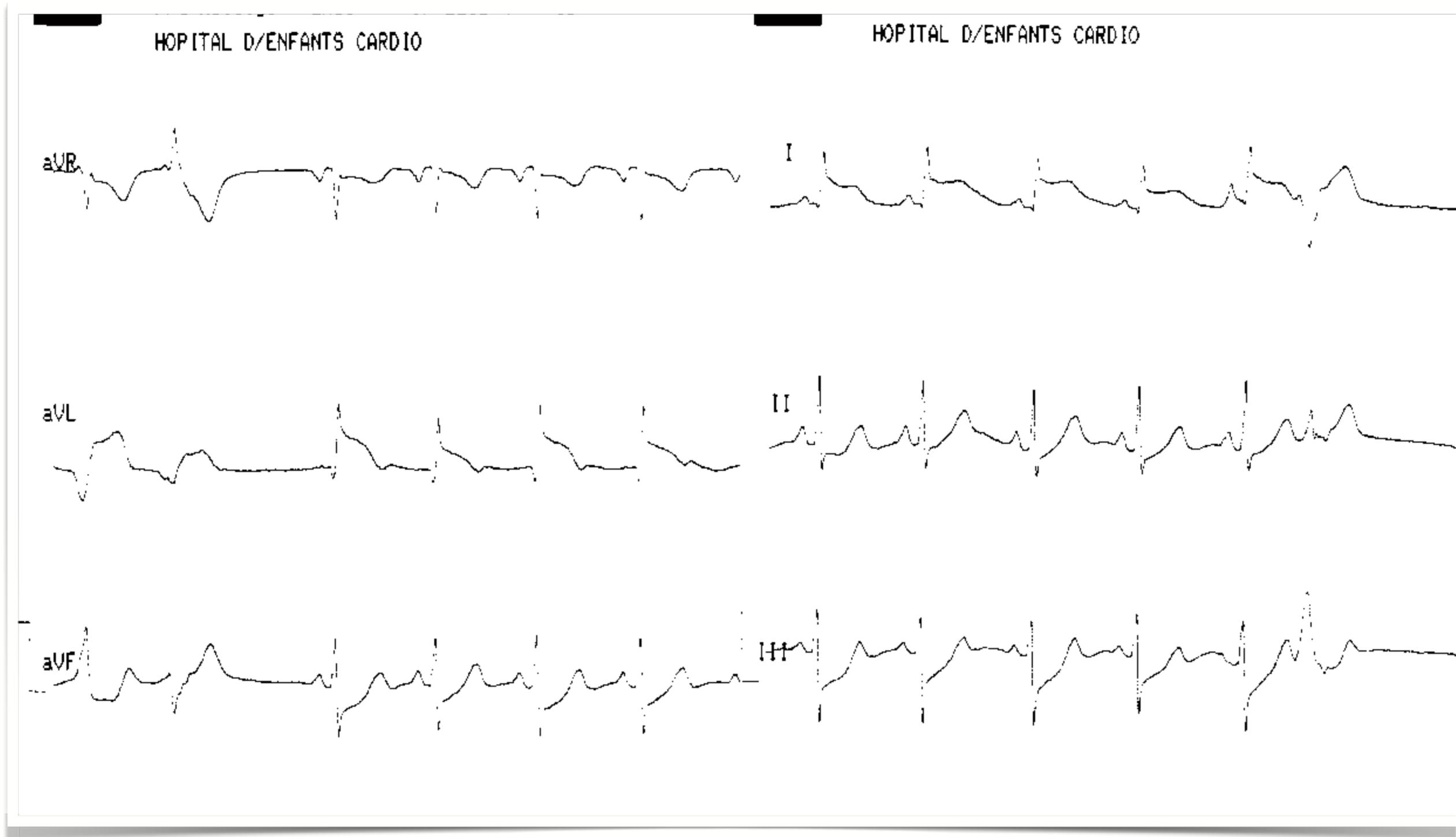
In Vivo Detection of Coronary Artery Anomalies in Asymptomatic Athletes by Echocardiographic Screening*

Paolo Zeppilli, MD; Antonio dello Russo, MD; Cesare Santini, MD;
Vincenzo Palmieri, MD; Luigi Natale, MD; Alessandro Giordano, MD; and
Andrea Frustaci, MD, FCCP

3/3150
0.09%

Pediatric Cardiology
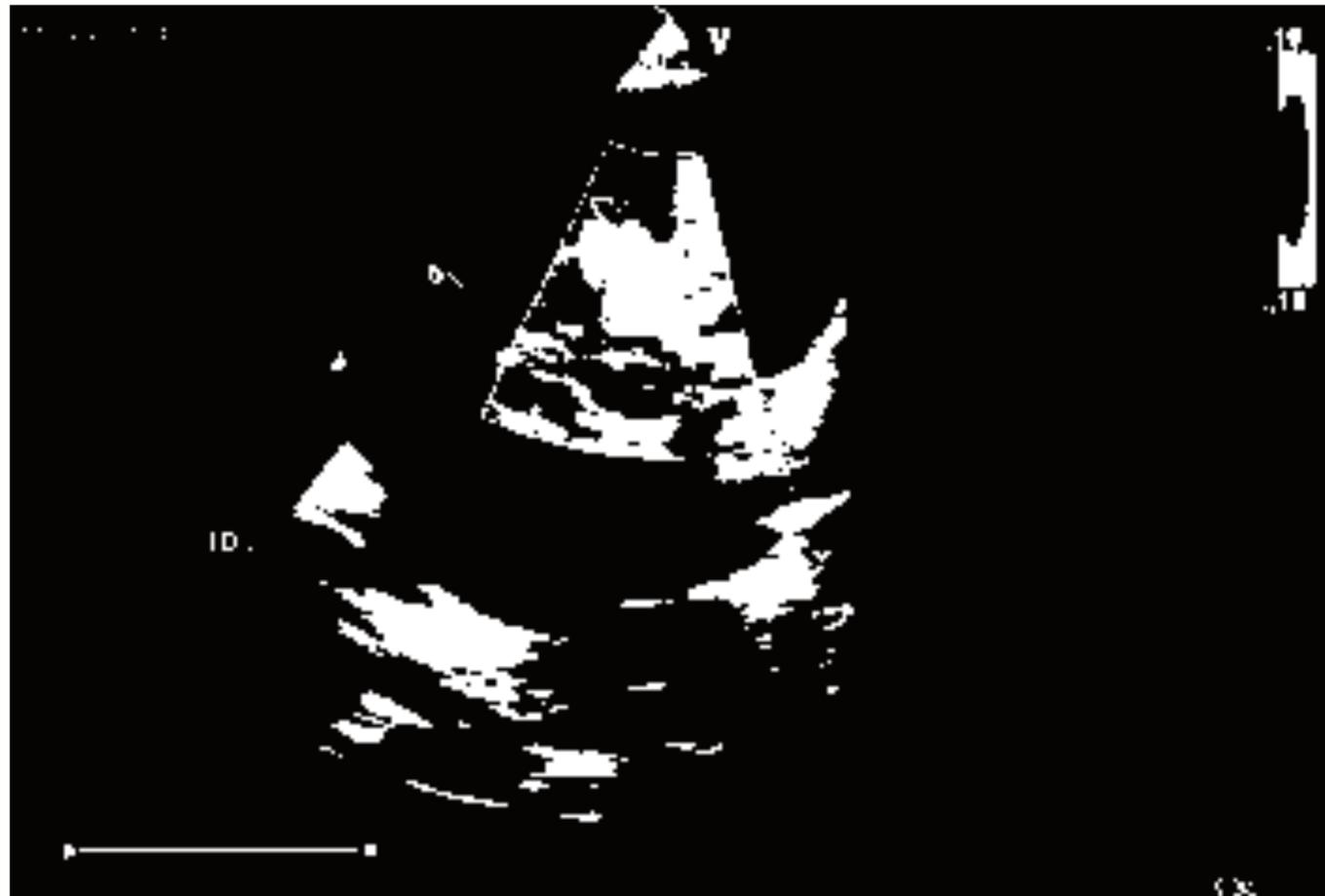
Major Coronary Artery Anomalies in a Pediatric Population: Incidence and Clinical Importance

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

Seattle, Washington

4/2388
0.17%

Left coronary artery from the right ostium with inter arterial course
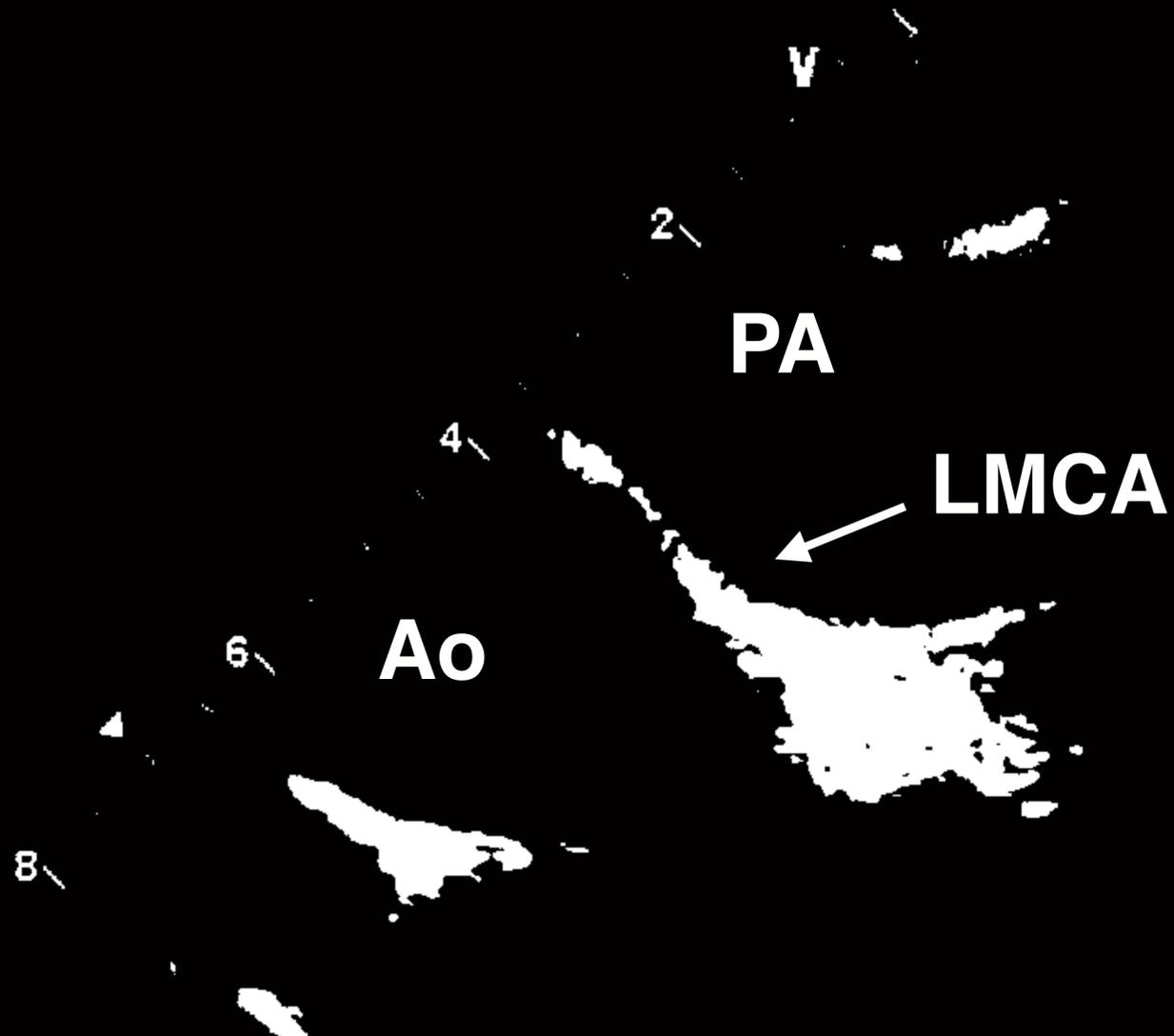
Left coronary artery from the right ostium with inter arterial course

Left coronary artery from the right ostium with inter arterial course

Left coronary artery from the right ostium with inter arterial course and intramural origin

RCA from left ostium
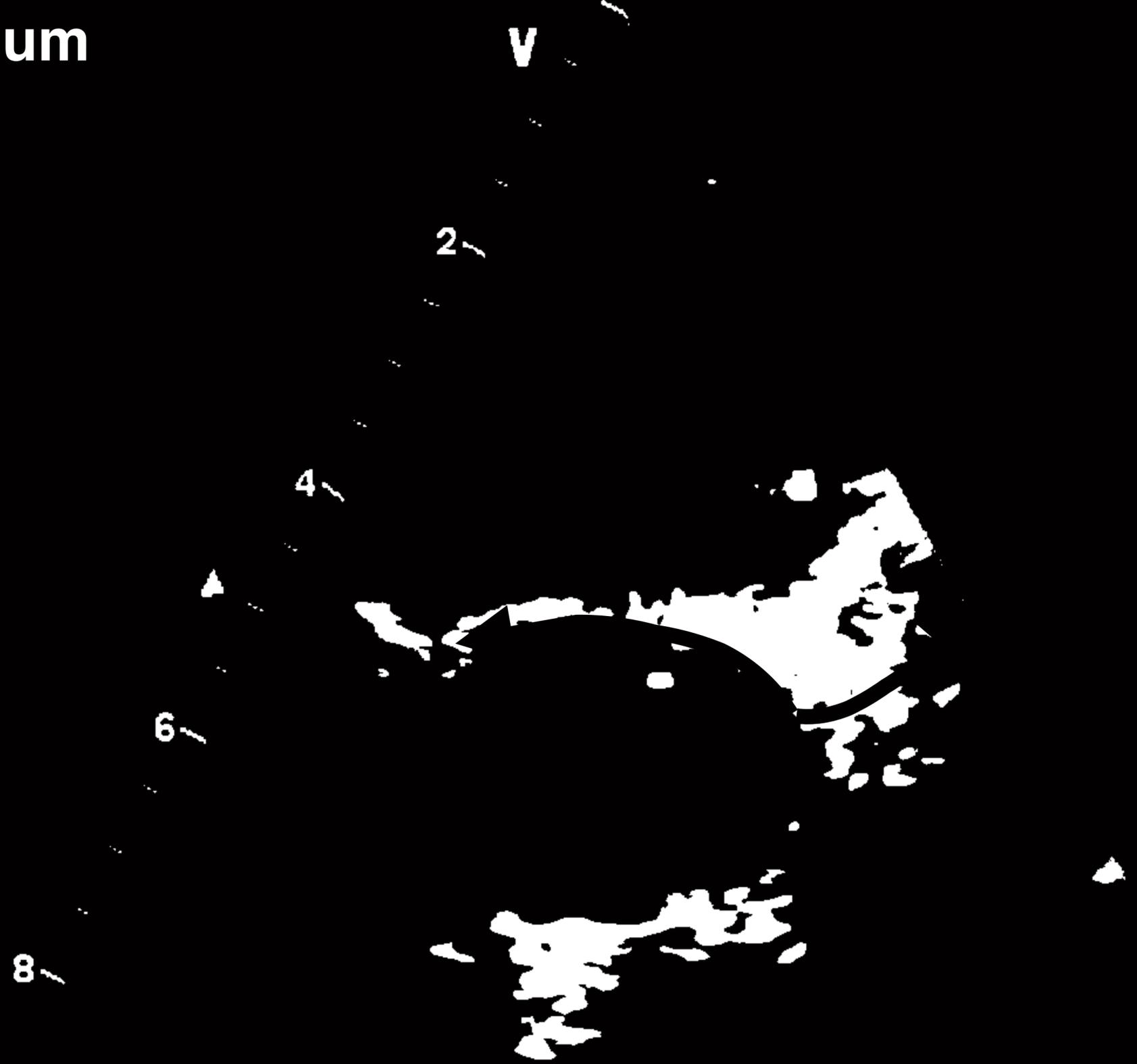
RCA from left ostium
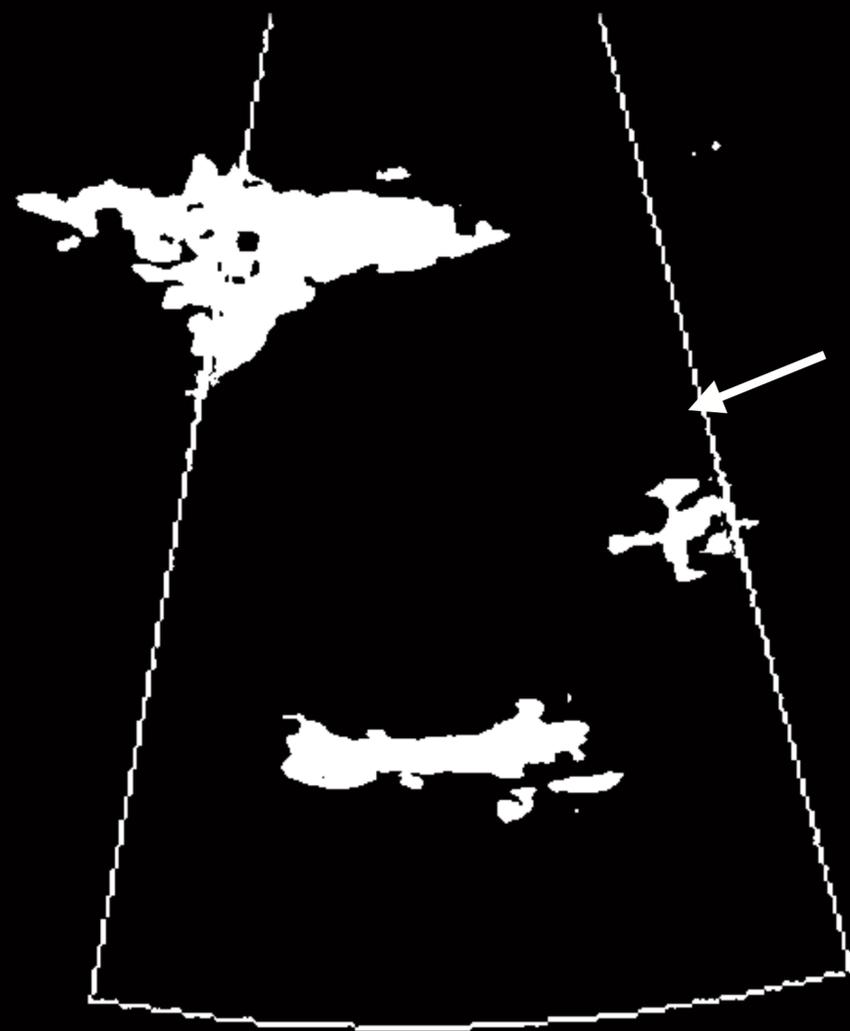
RCA with inter arterial course
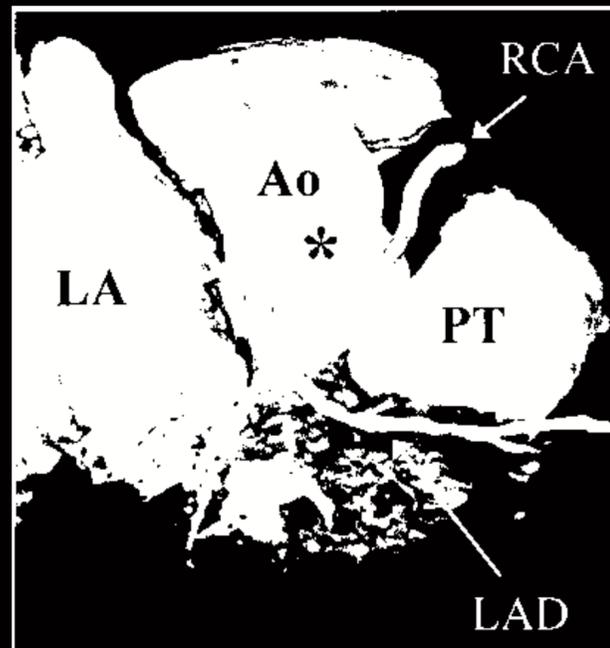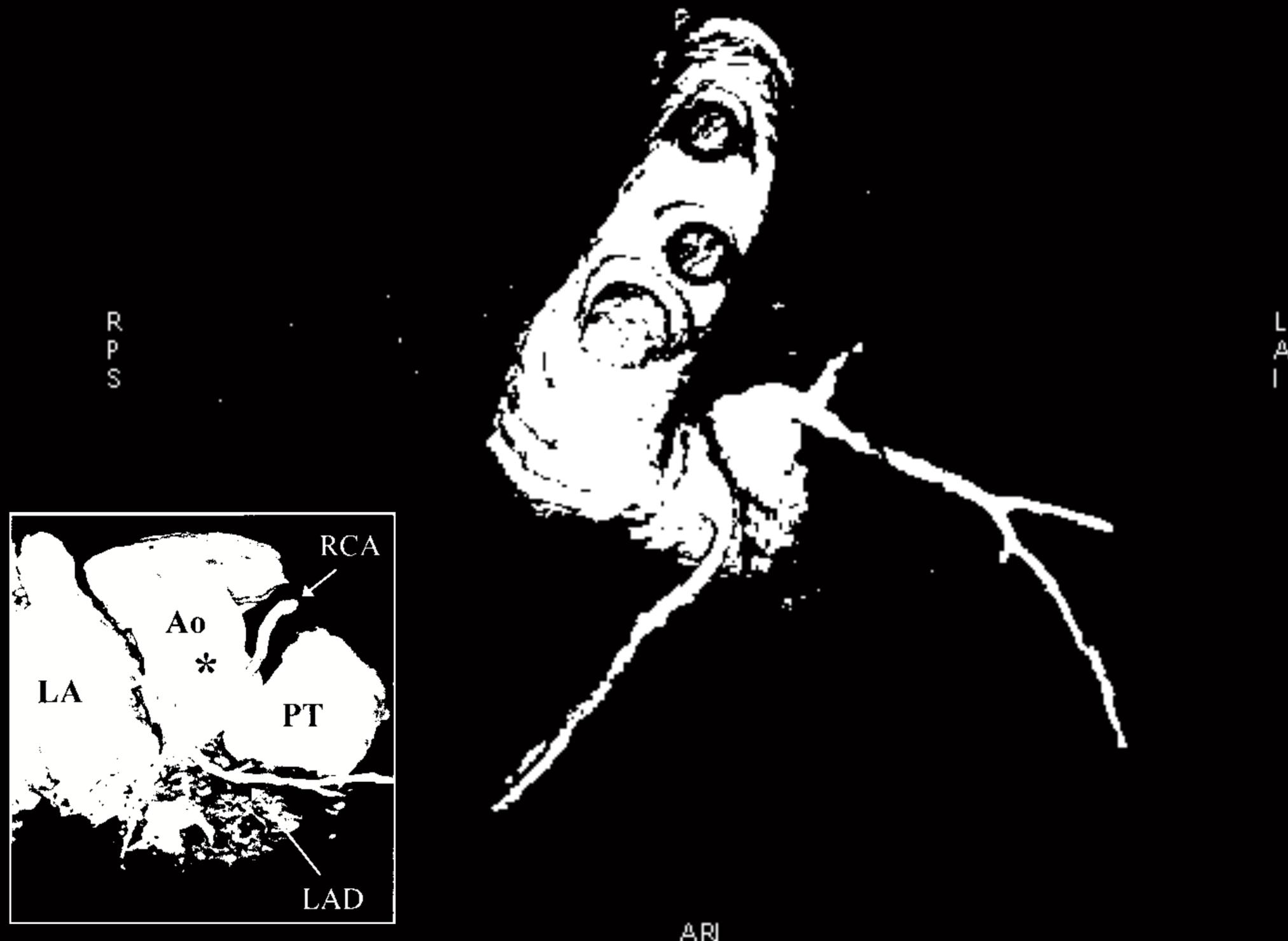
Unroofing
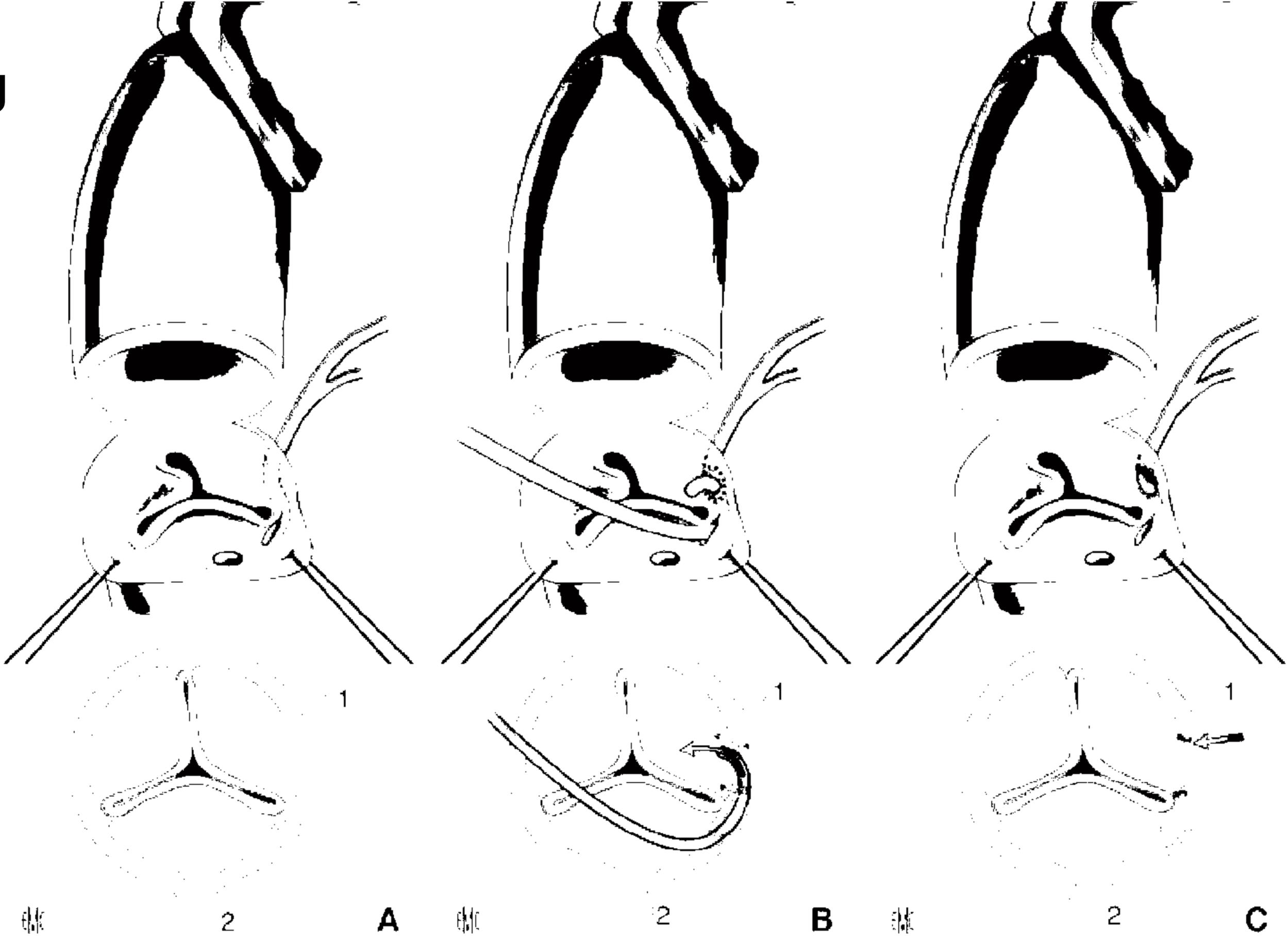
Anatomical repair
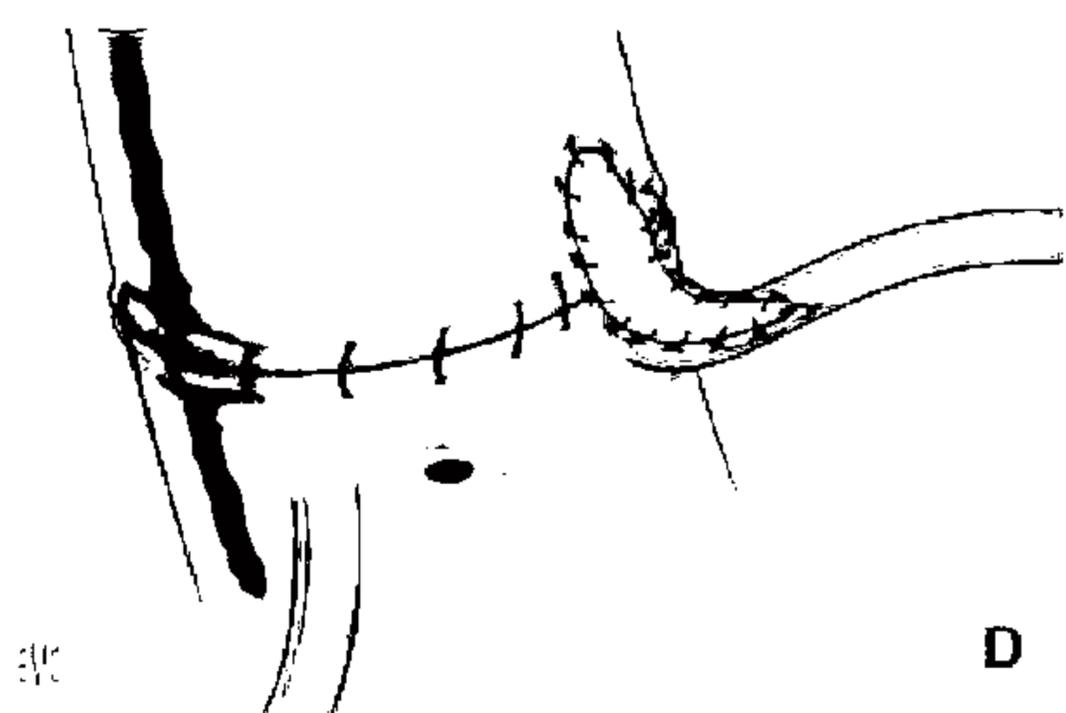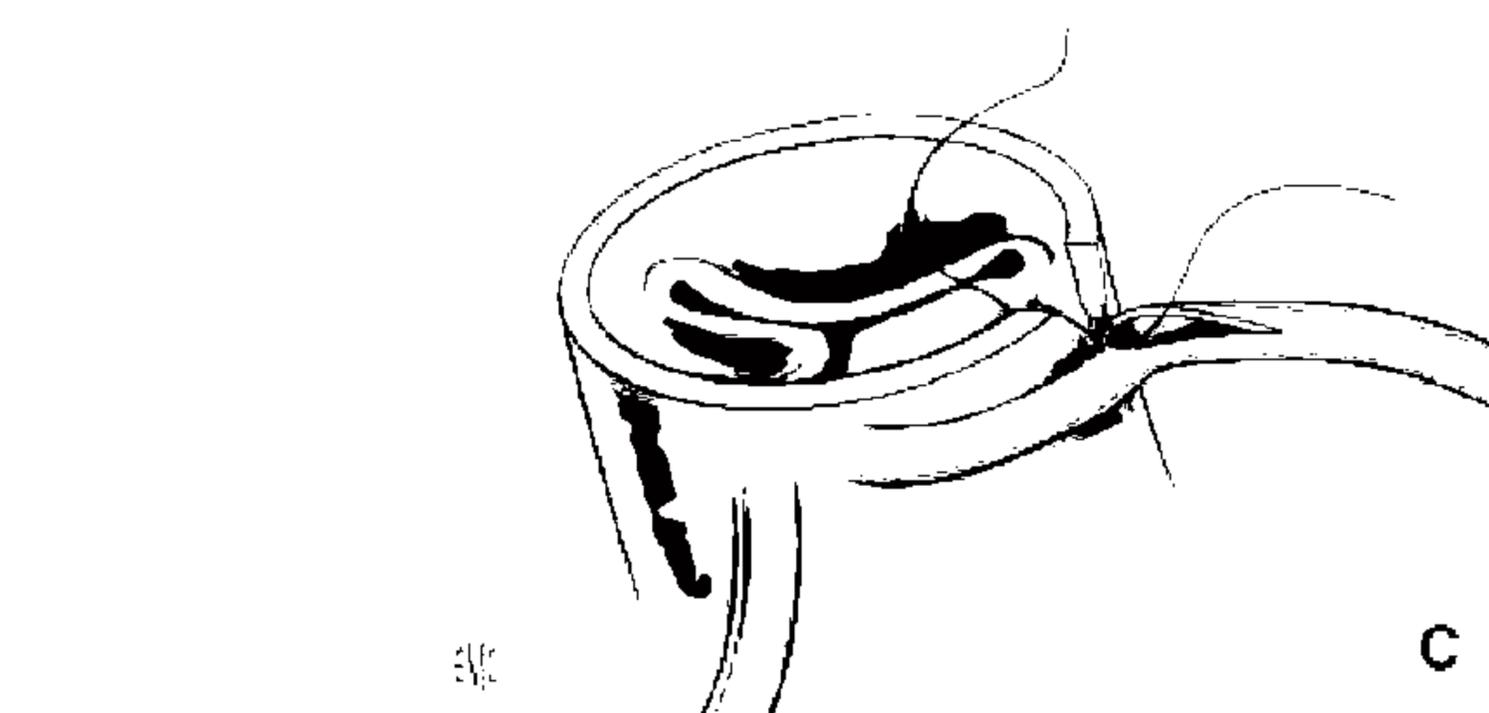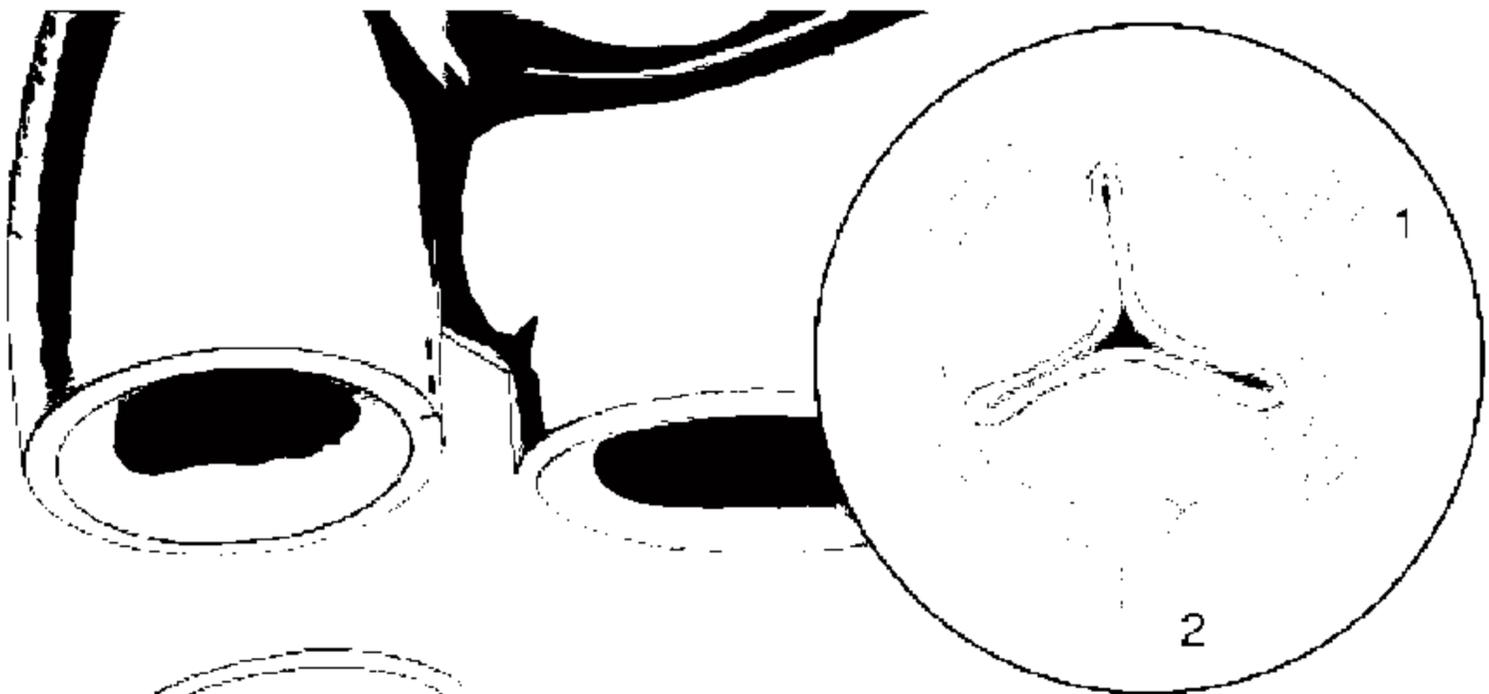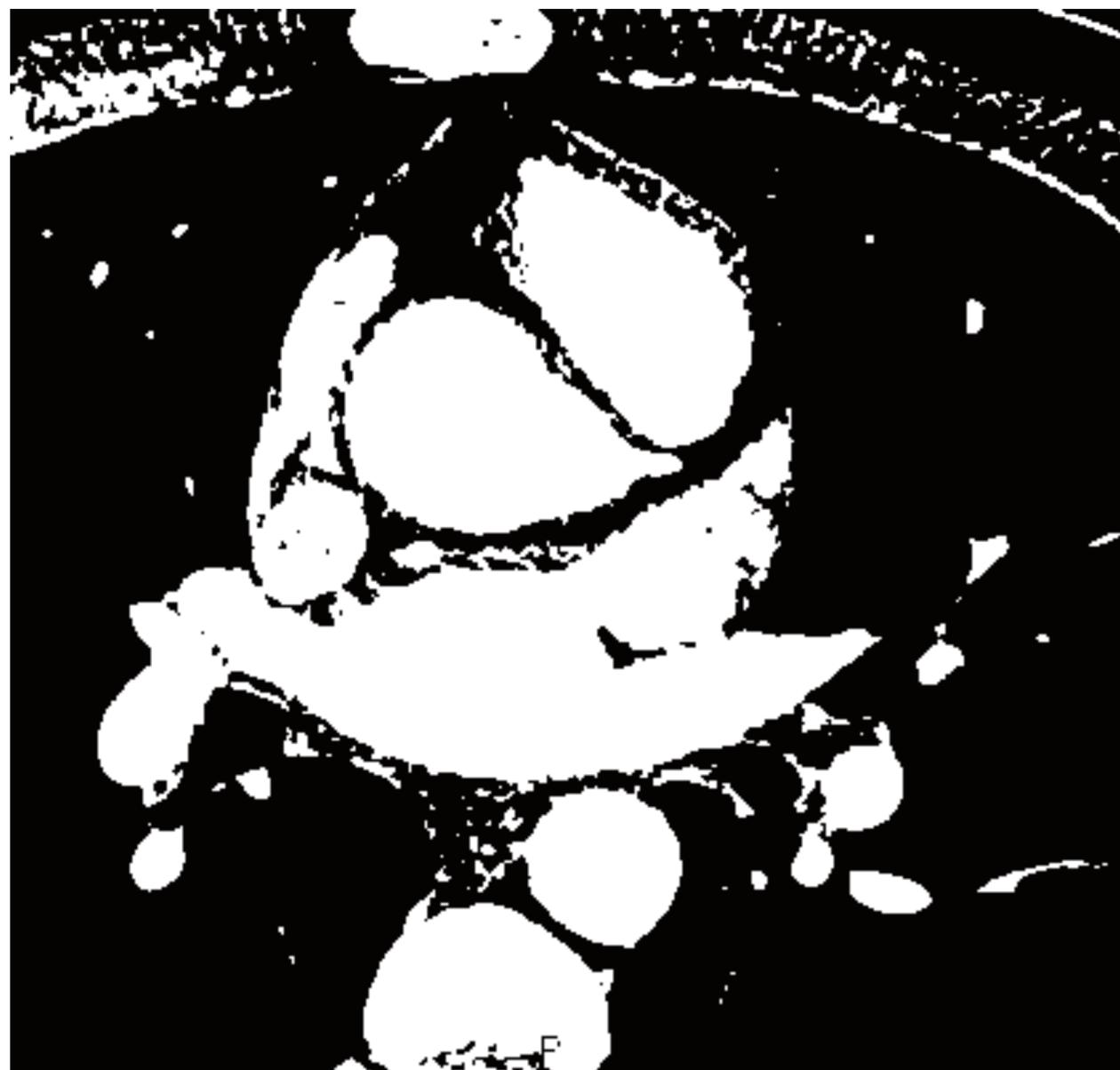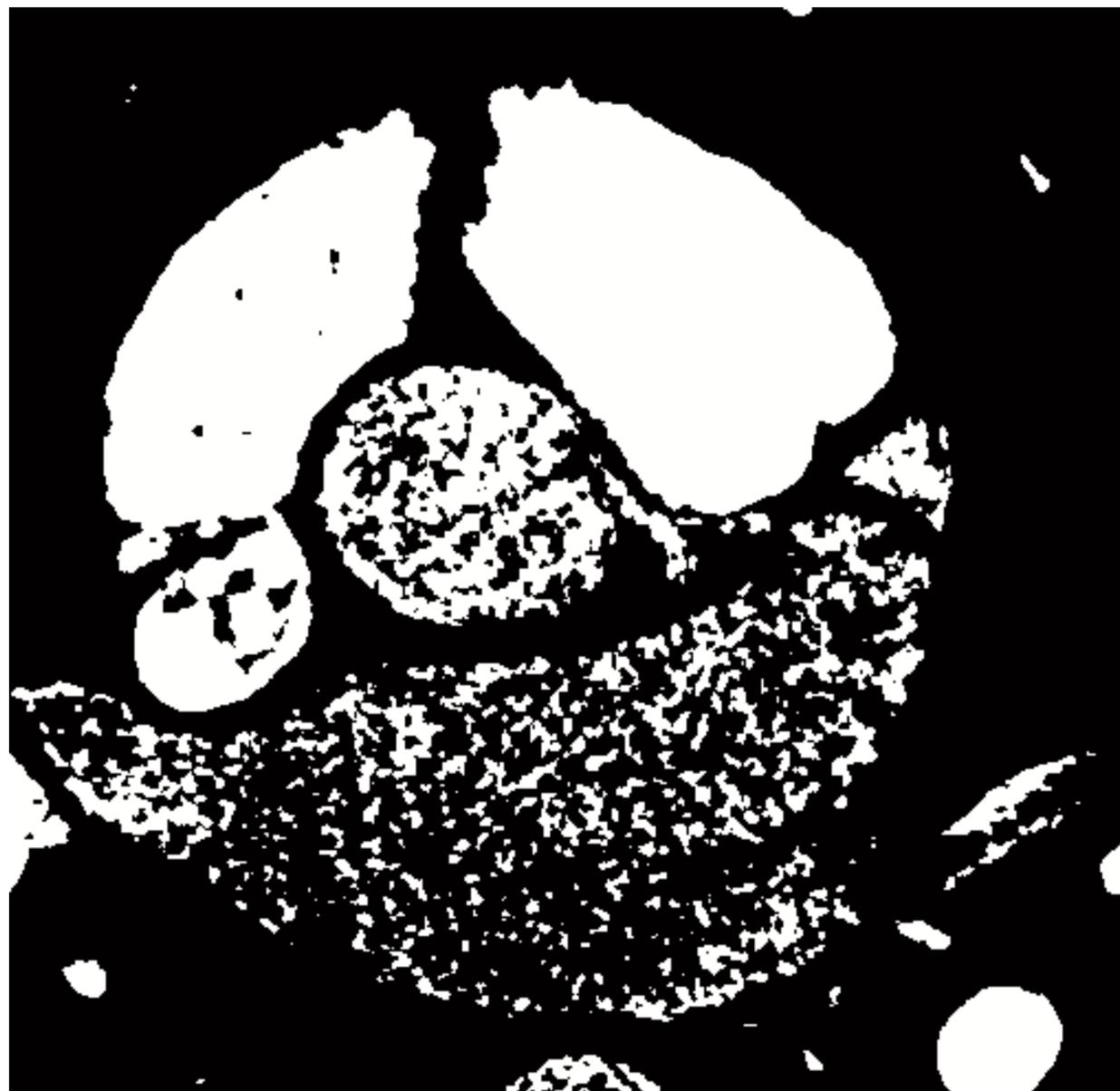
Septal course of LAD in the conal septum
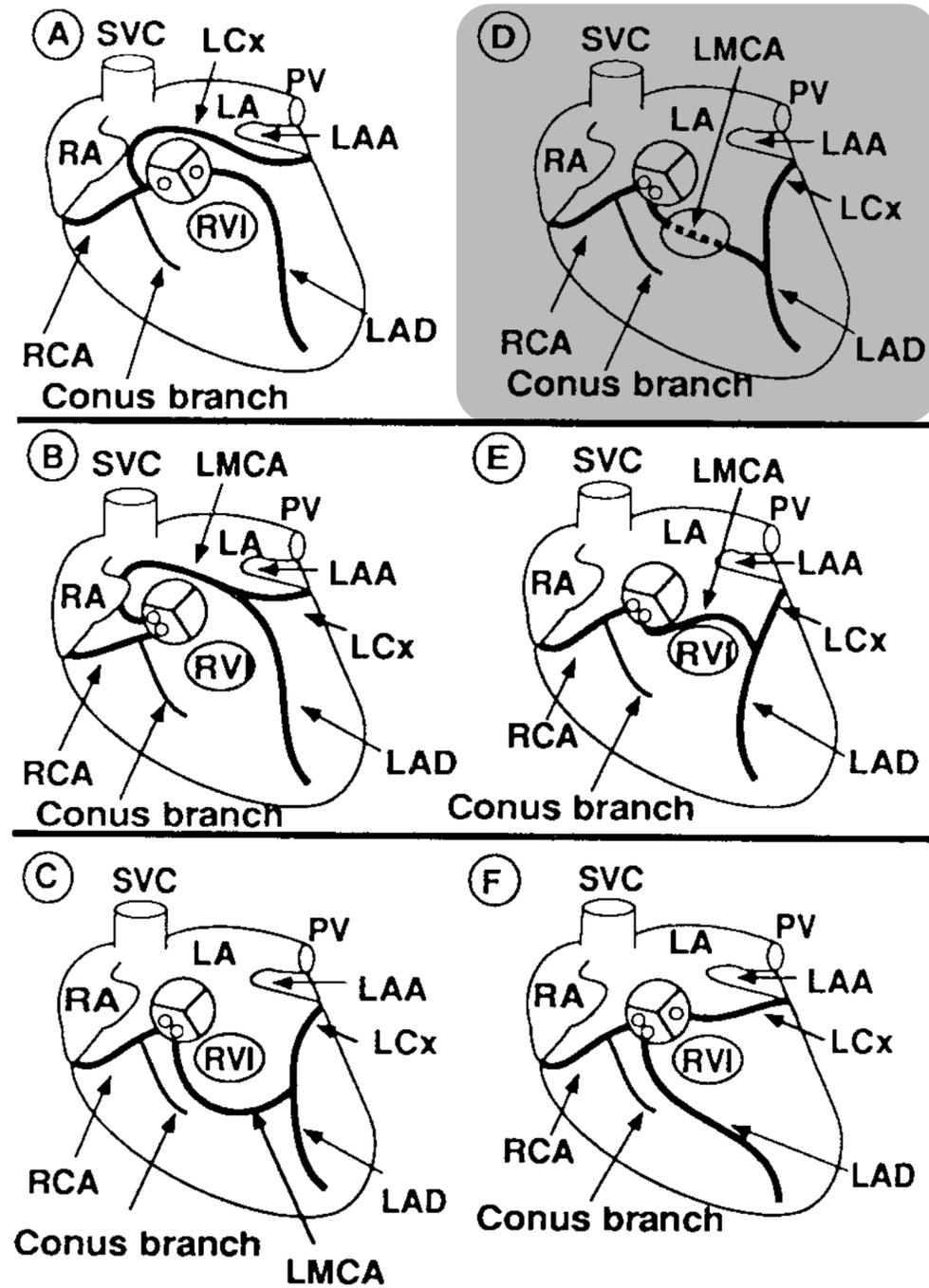
Abnormal origin of coronary arteries from the pulmonary artery

Abnormal origin from the pulmonary artery : ALCAPA
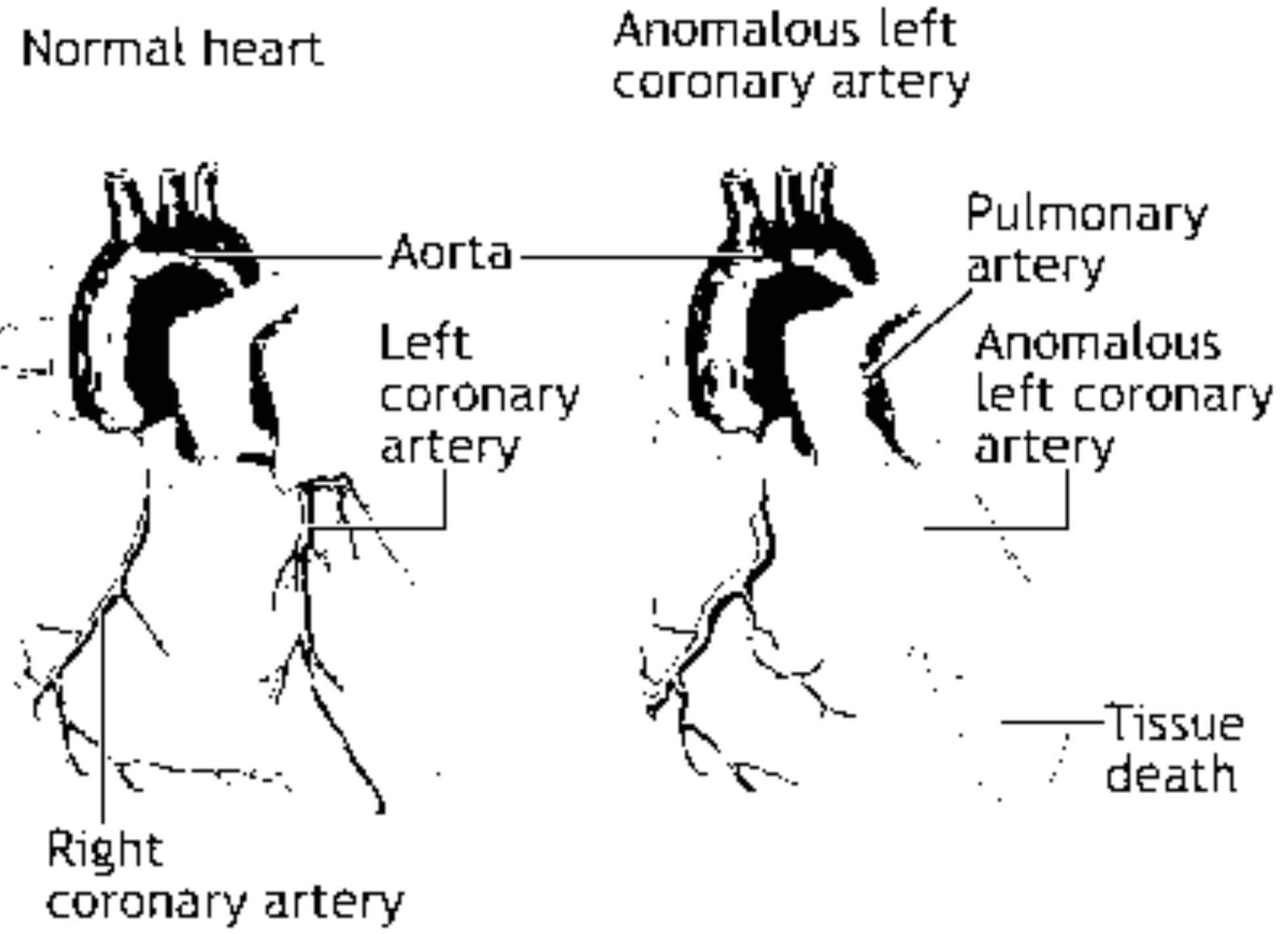
Normal heart

Anomalous left coronary artery

Aorta

Left coronary artery

Right coronary artery

Pulmonary artery

Anomalous left coronary artery

Tissue death

Abnormal origin from the pulmonary artery : ALCAPA
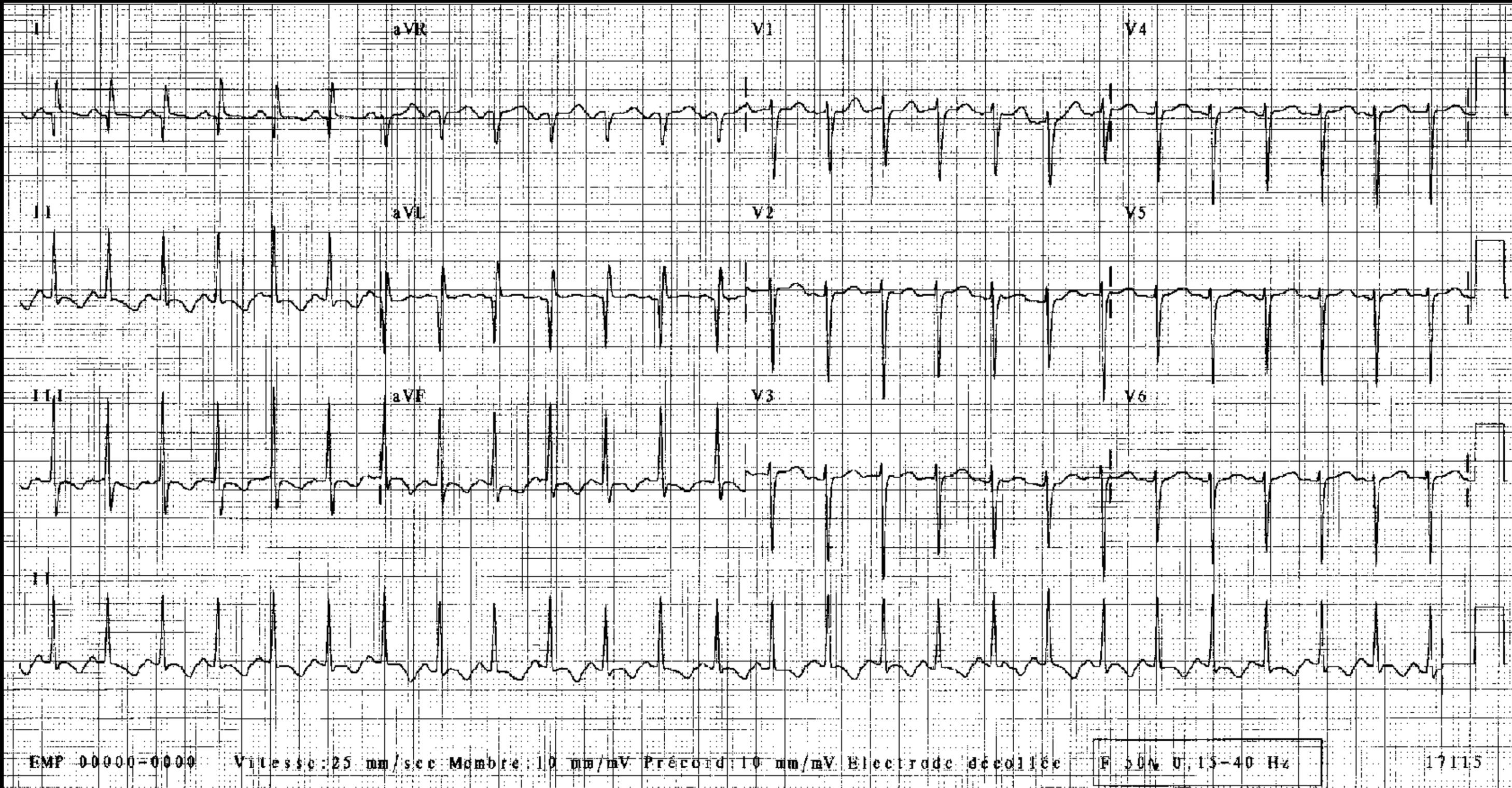
Abnormal origin from the pulmonary artery : ALCAPA
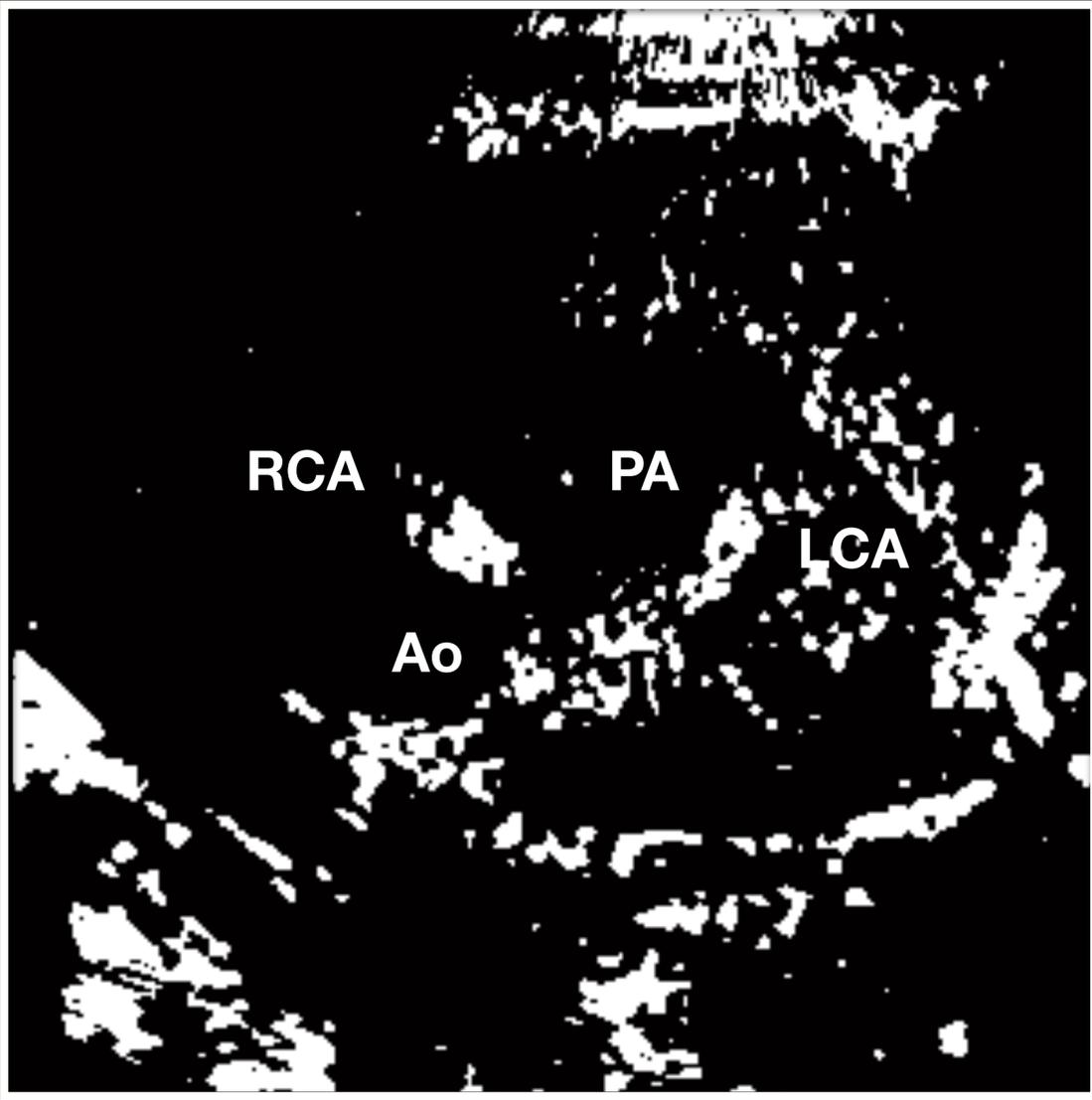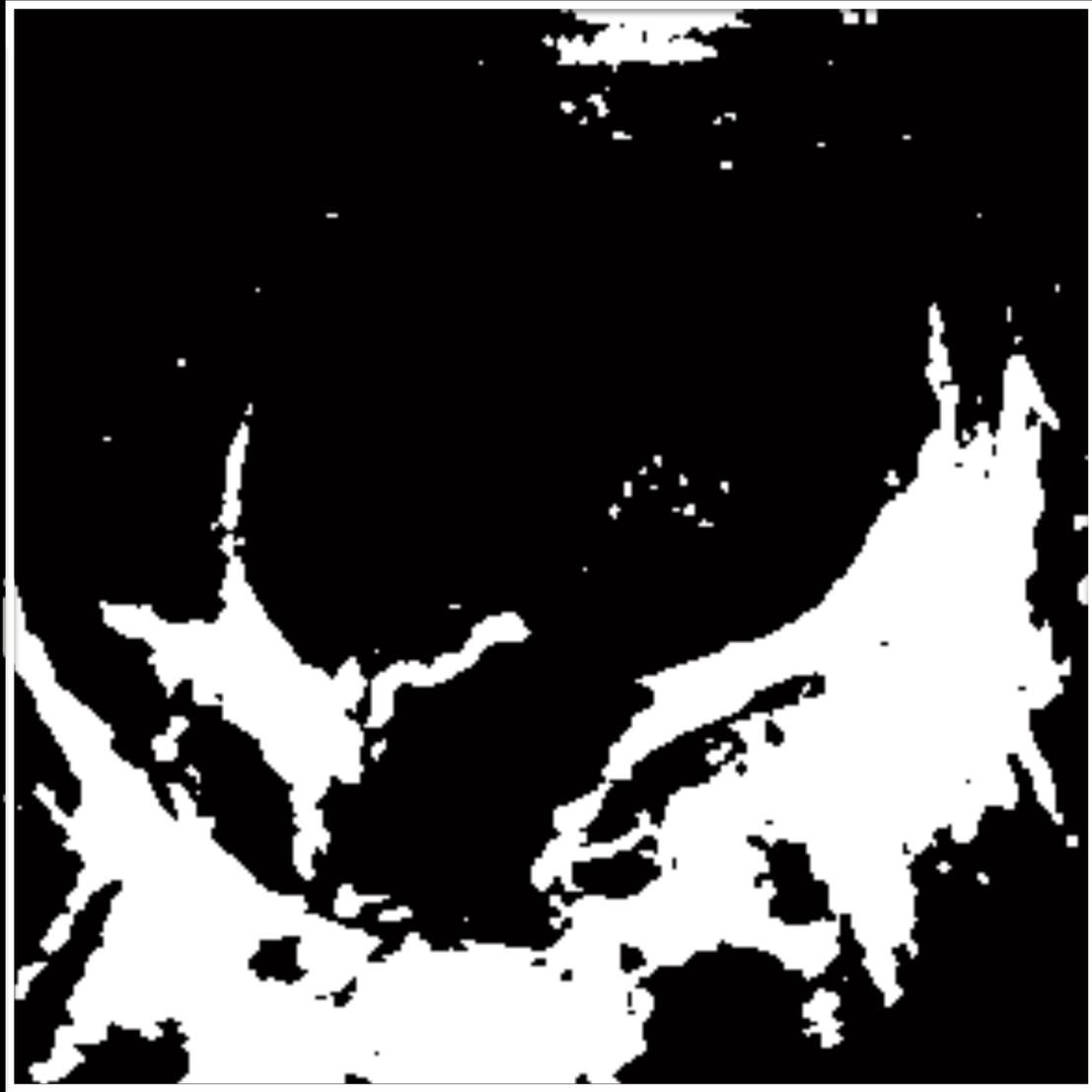
Abnormal origin from the pulmonary artery : ALCAPA
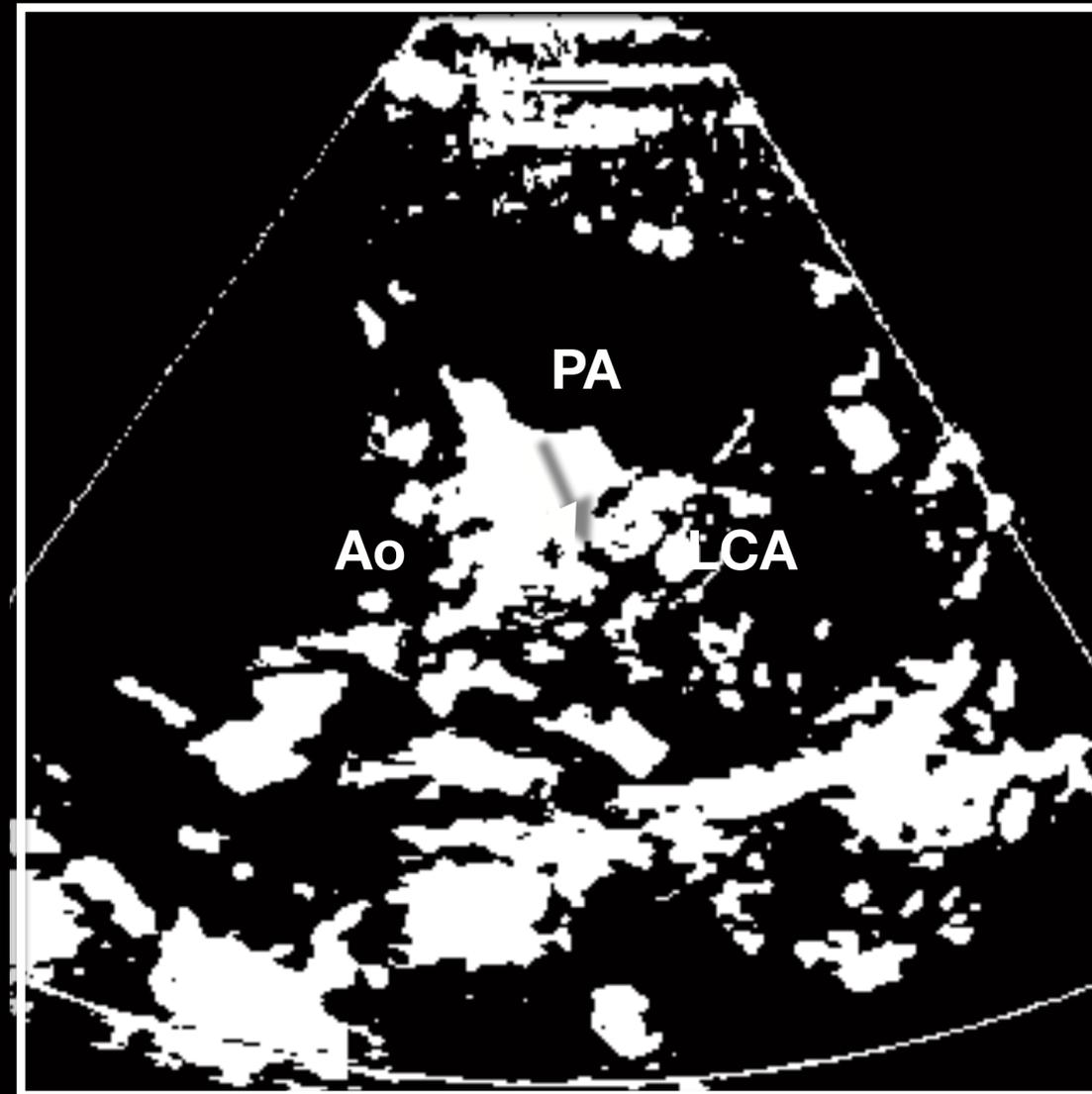
Abnormal origin from the pulmonary artery : ALCAPA

Abnormal origin from the pulmonary artery : ALCAPA
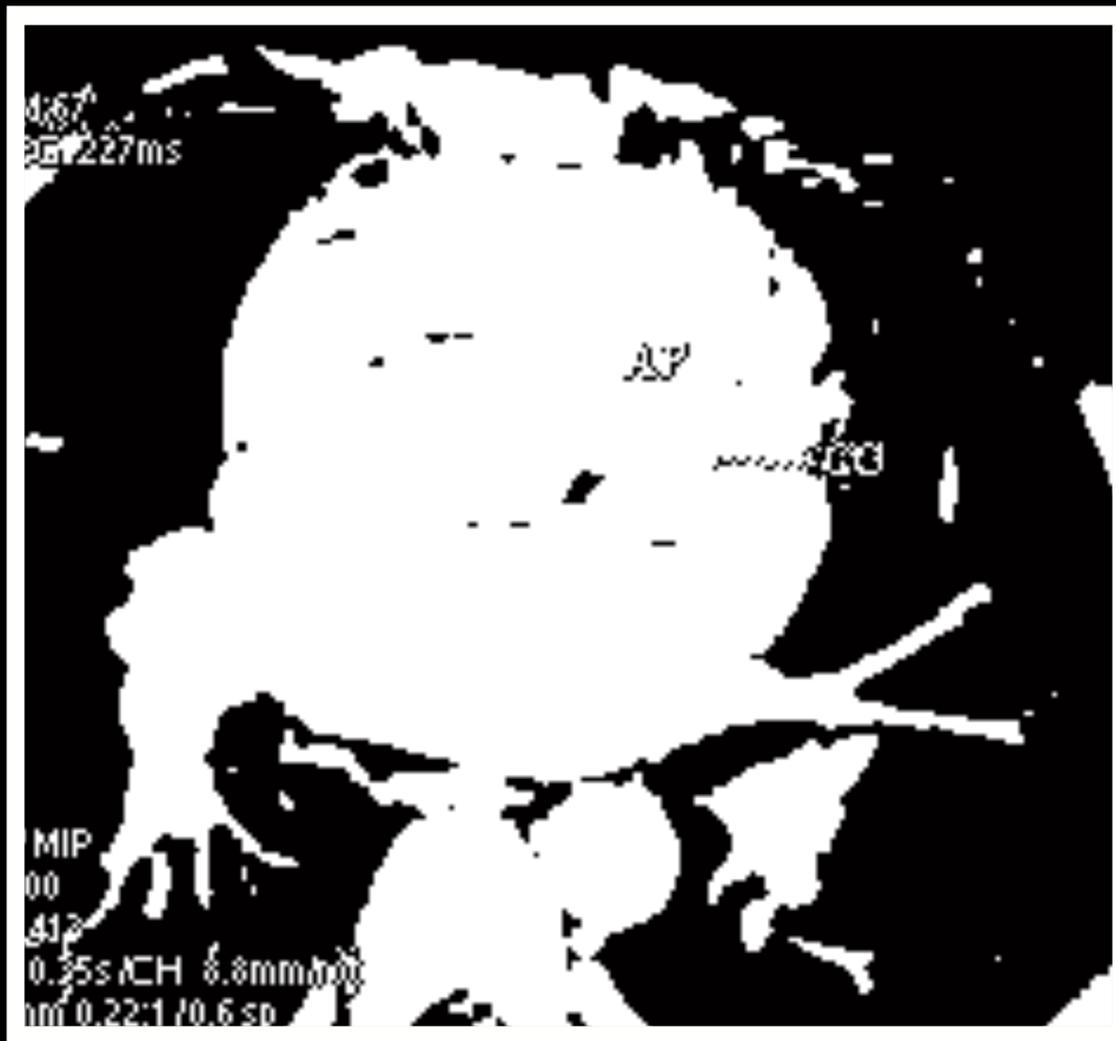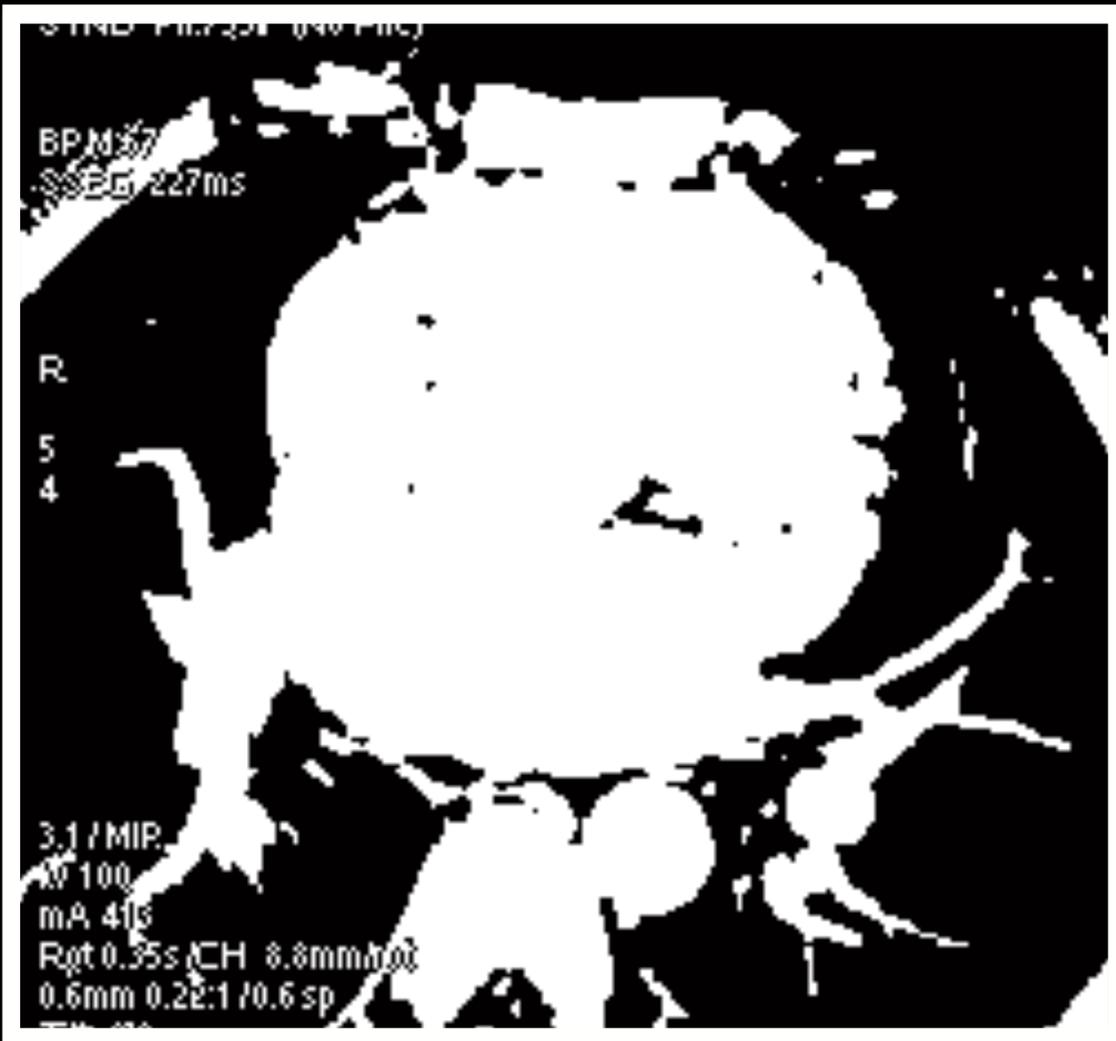
Abnormal origin from the pulmonary artery : ARCAPA
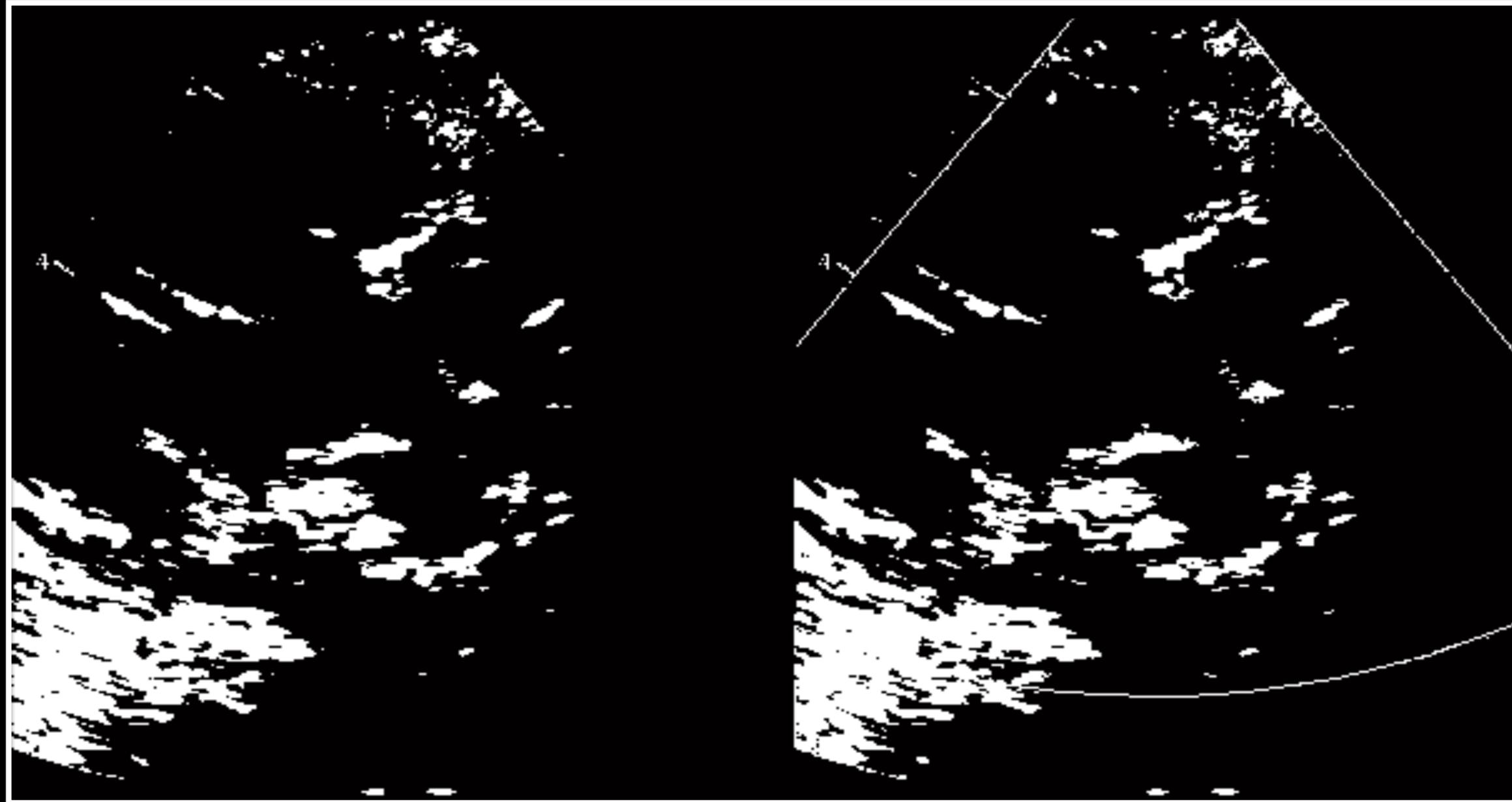
Abnormal origin from the pulmonary artery : ARCAPA
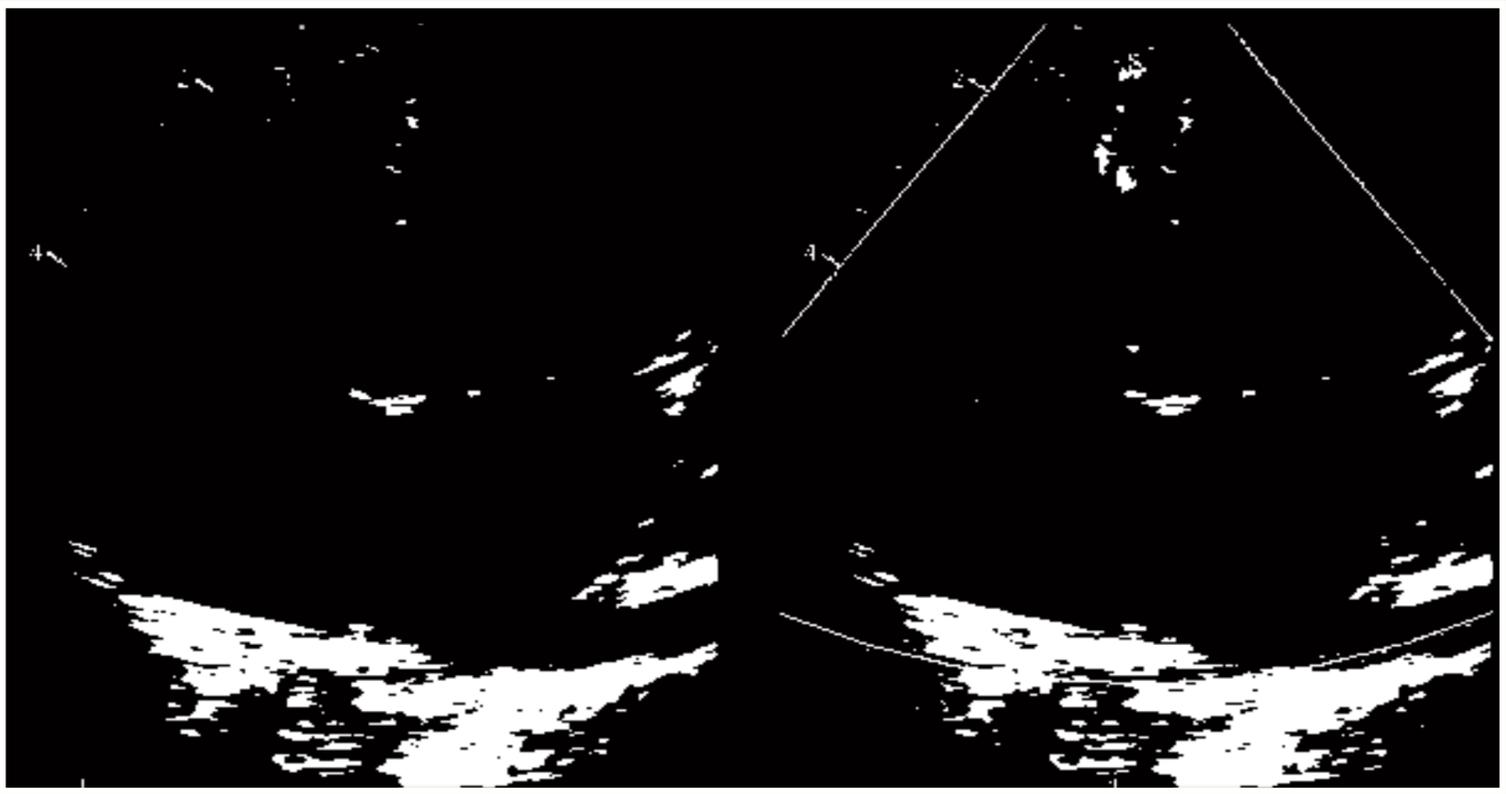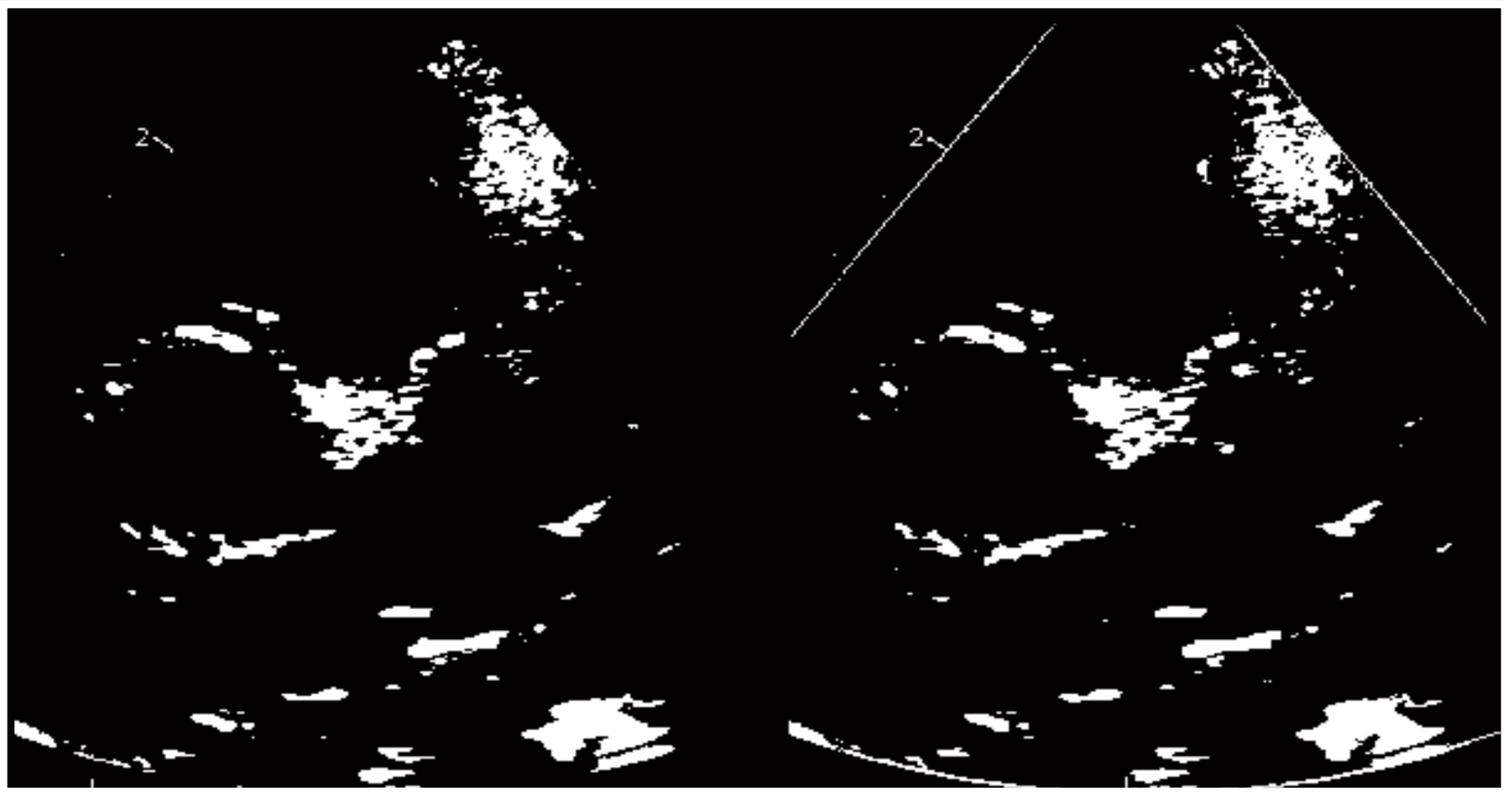
Abnormal origin from the pulmonary artery : ALCAPA surgery
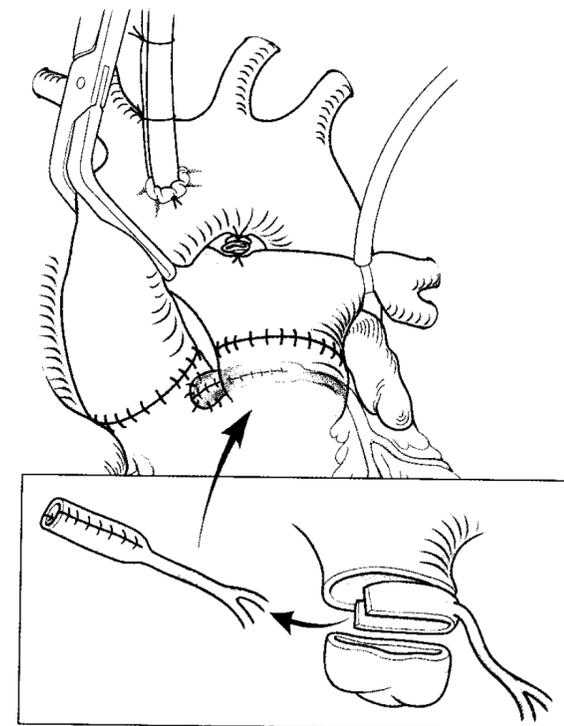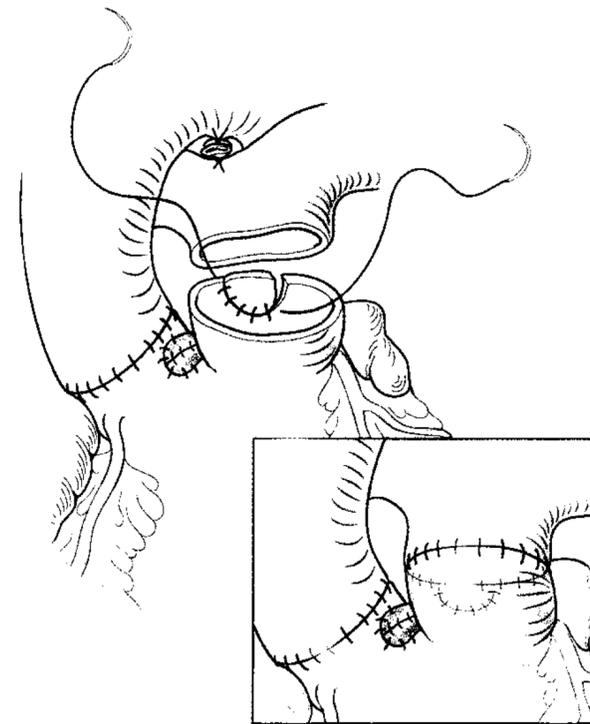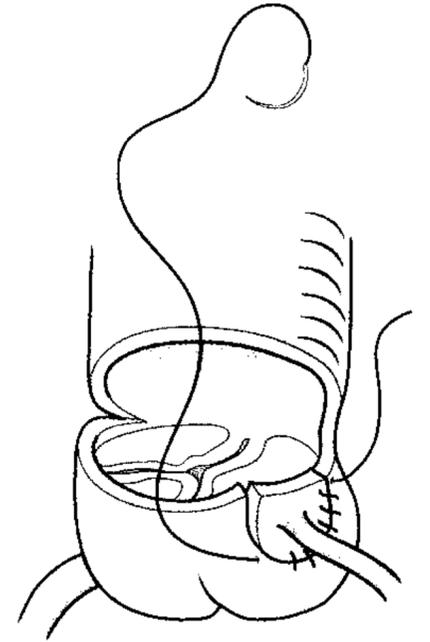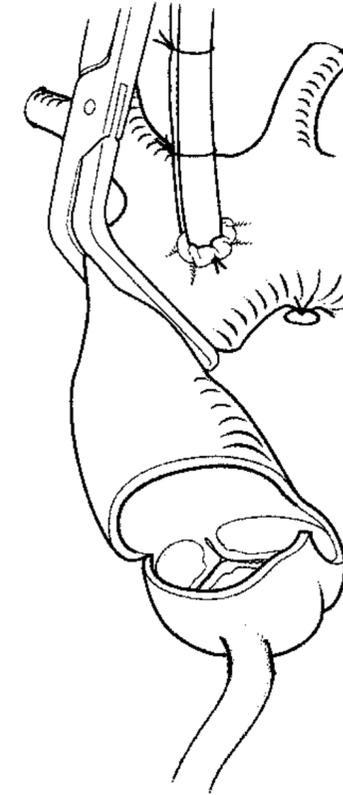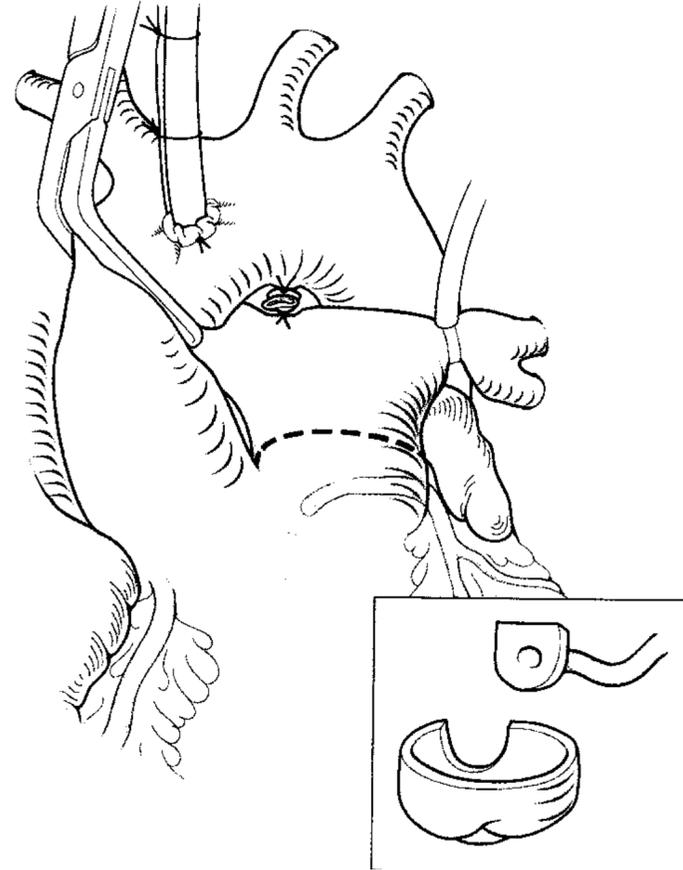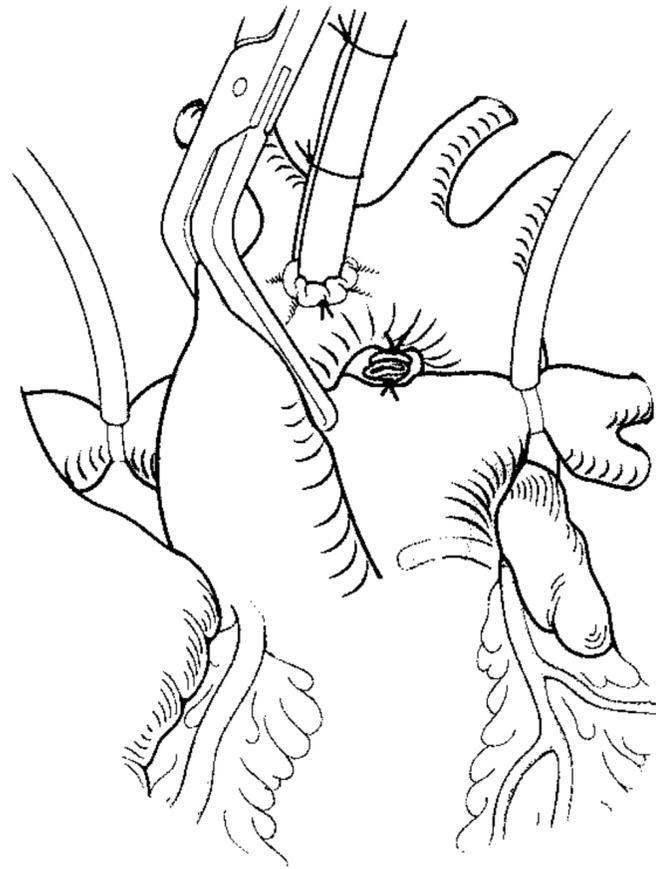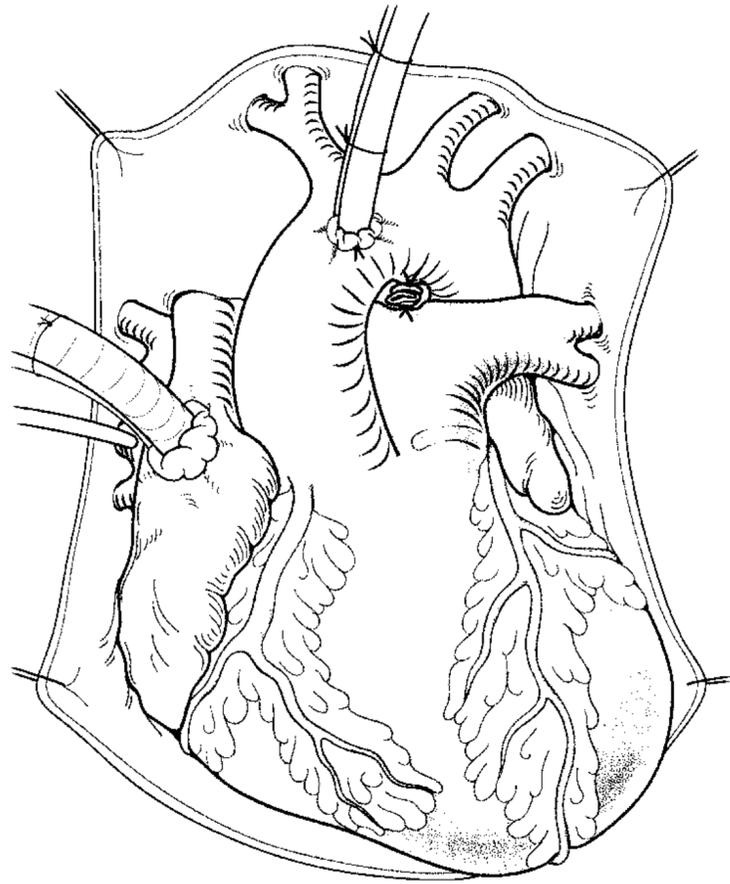
Abnormal origin from the pulmonary artery : ALCAPA
Mitral regurgitation

Coronary fistulae

Coronary fistulae

Coronary fistulae

A   B   C
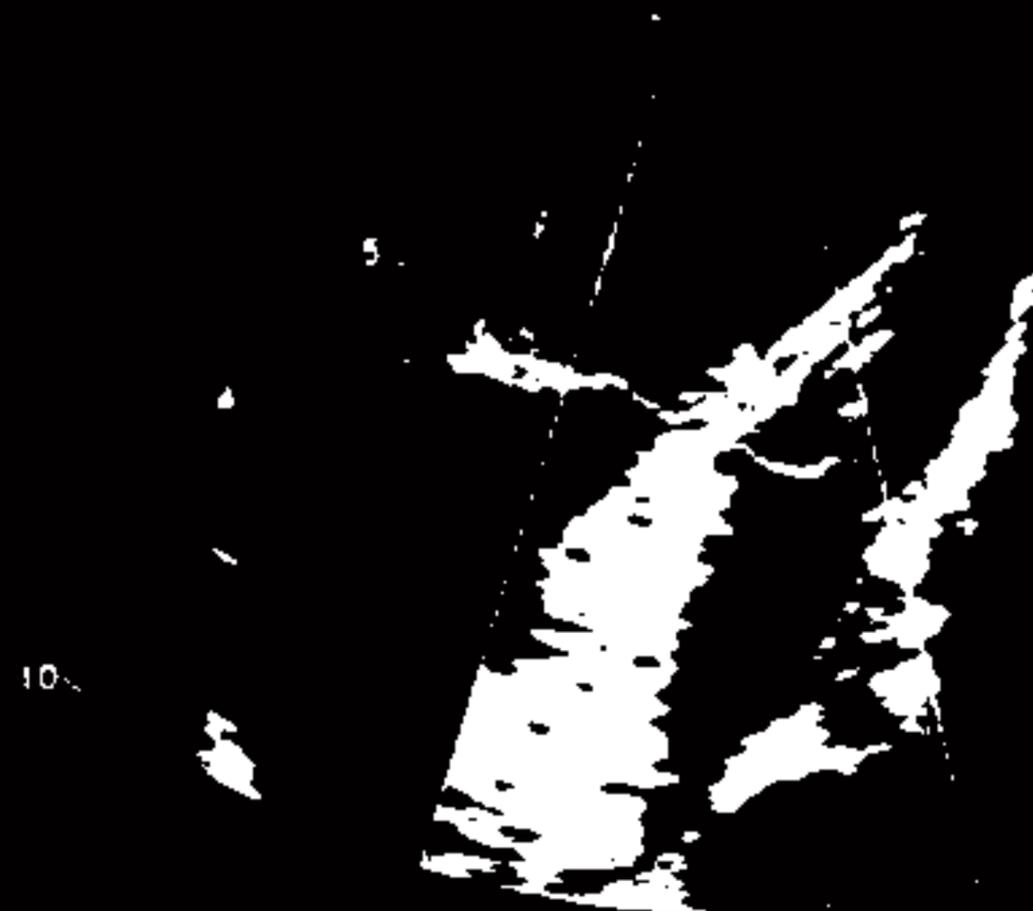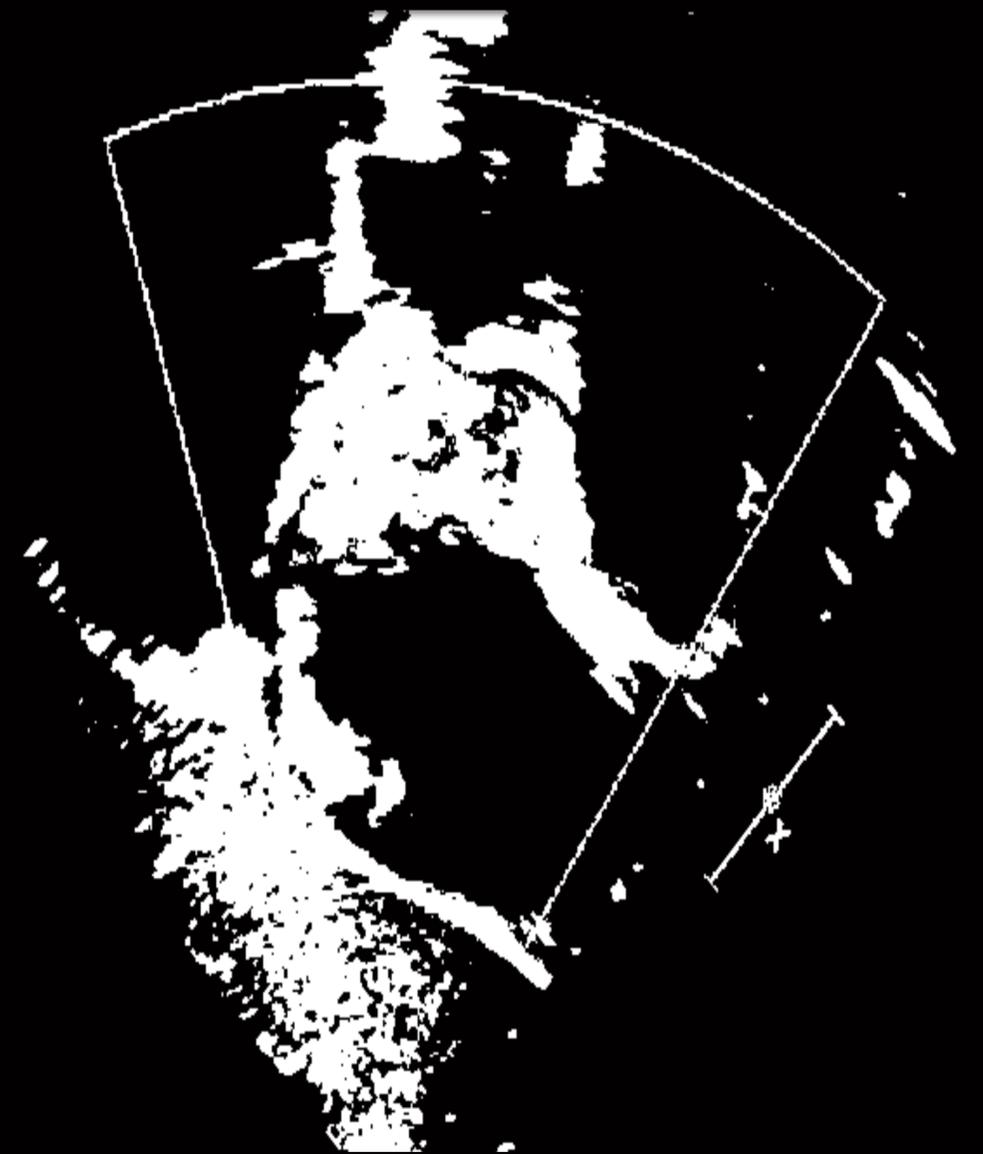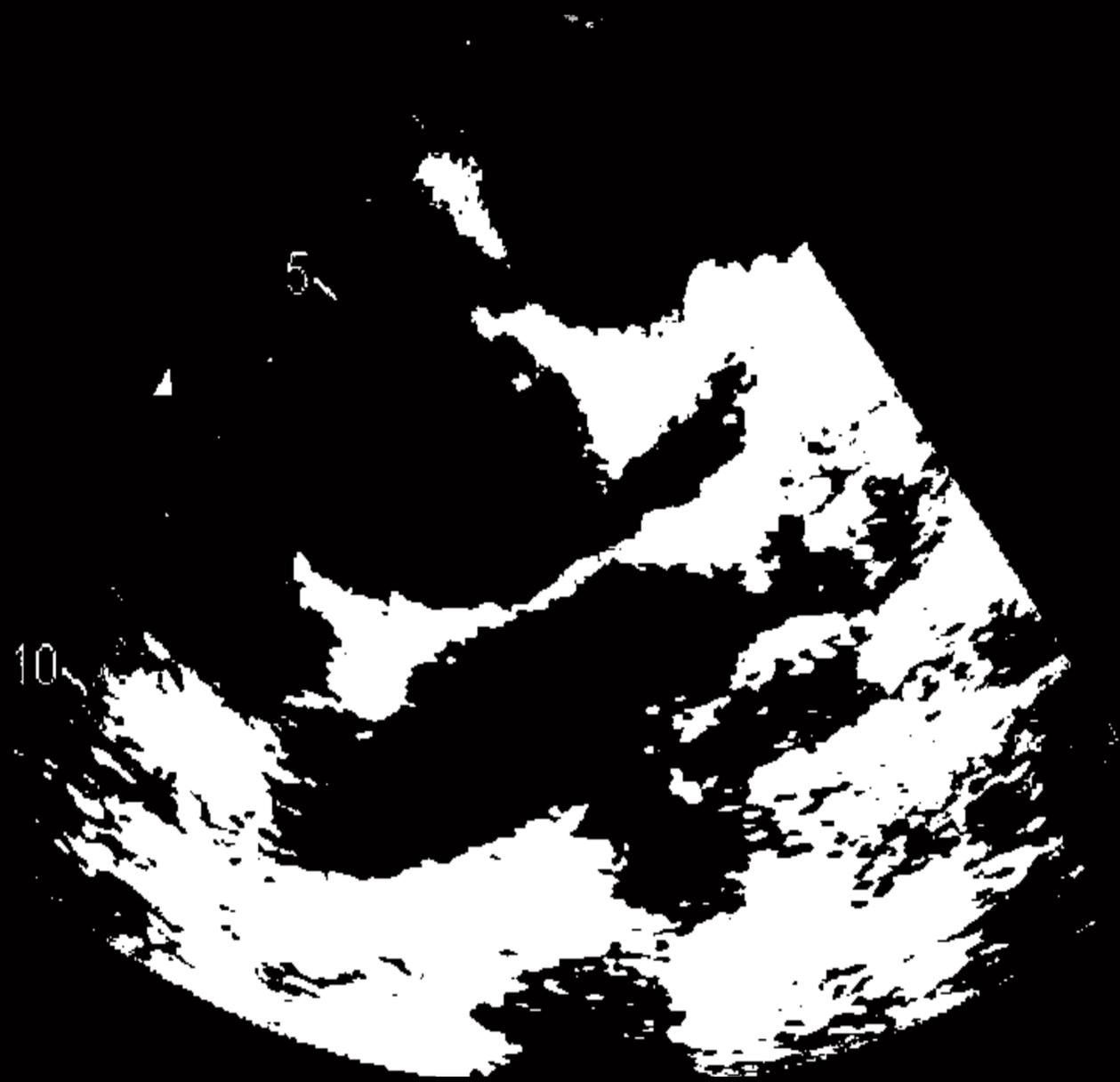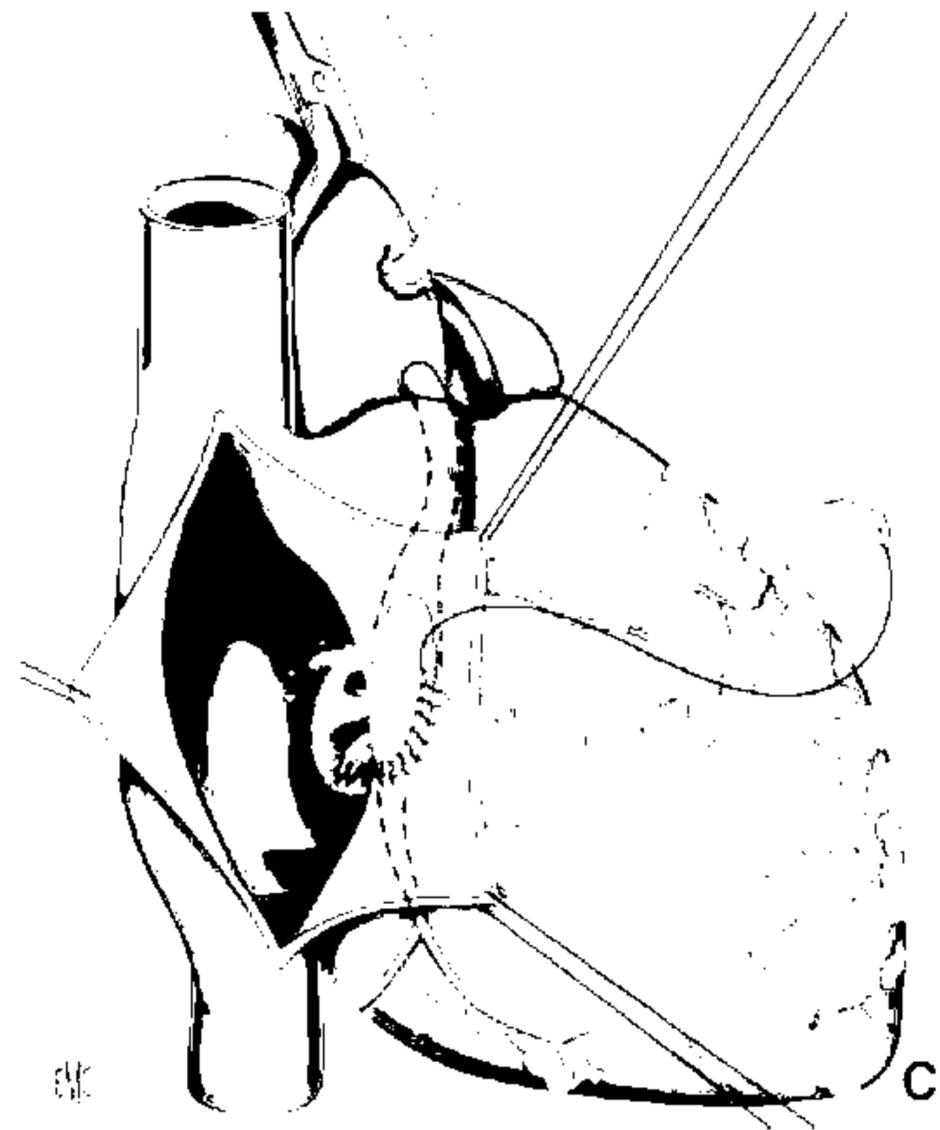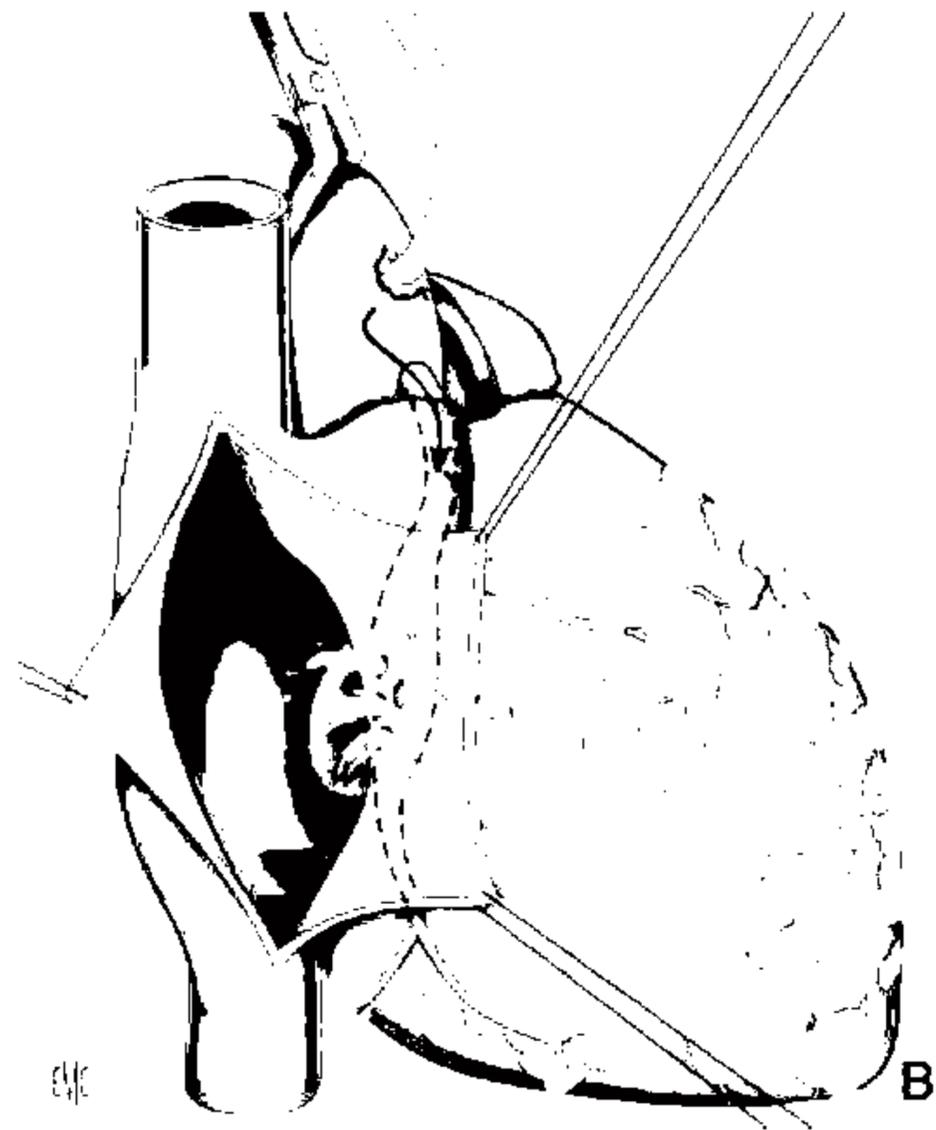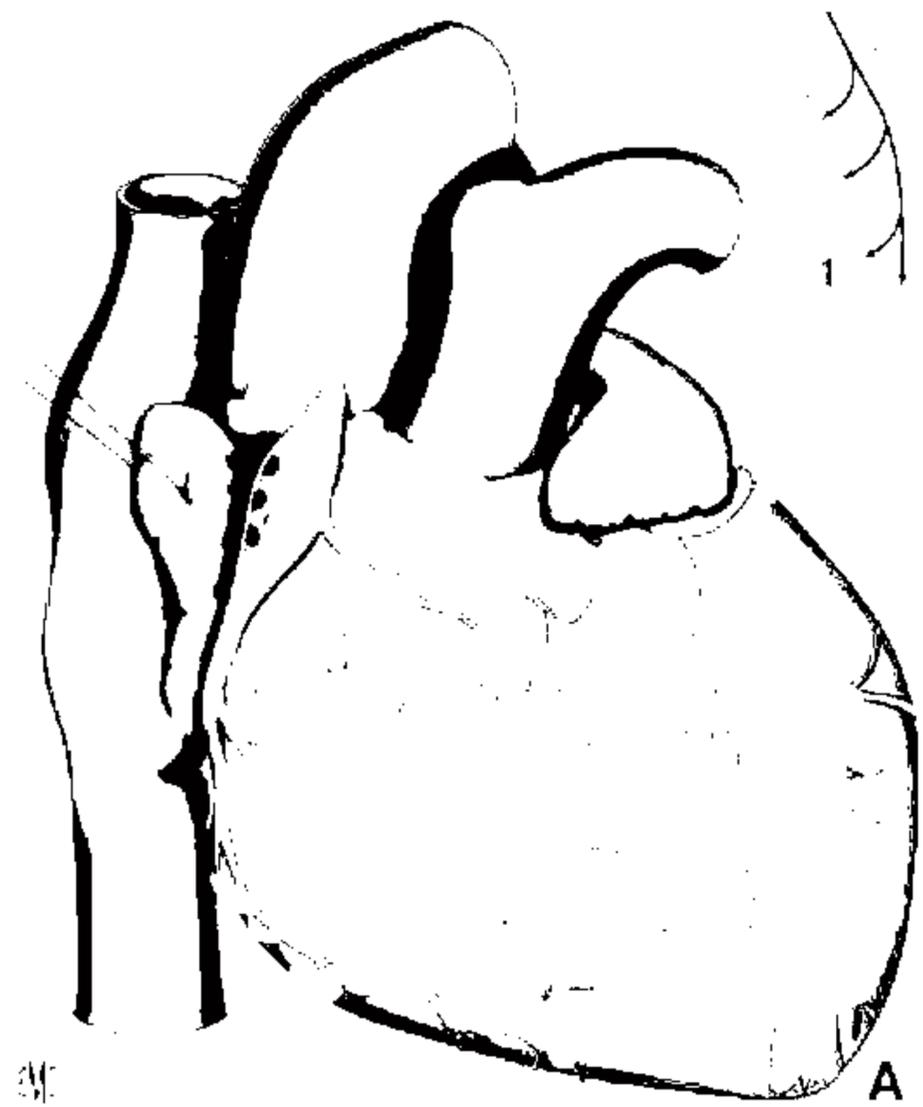
Coronary fistulae in PA-IVS & HLHS
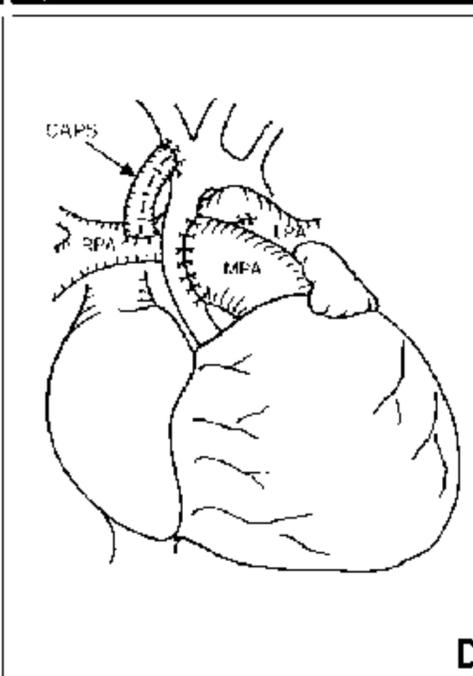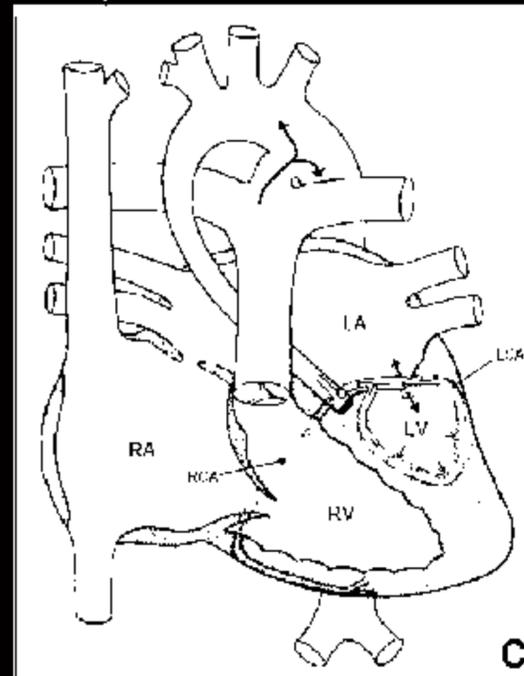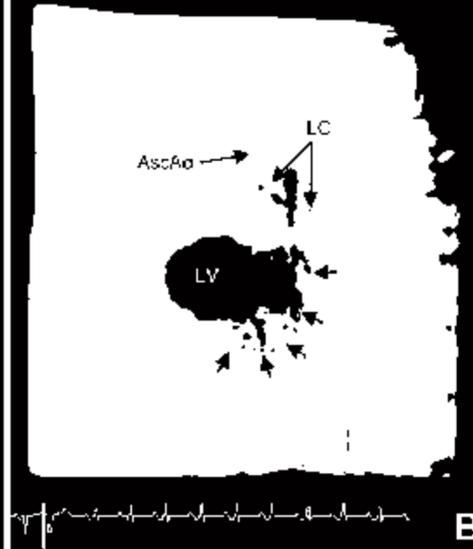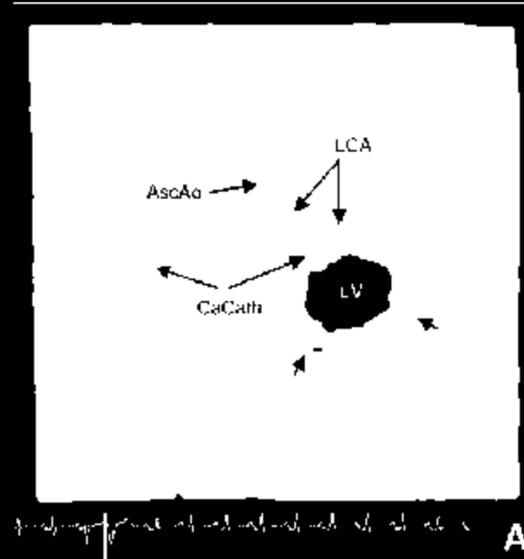
Rares anomalies

GACI
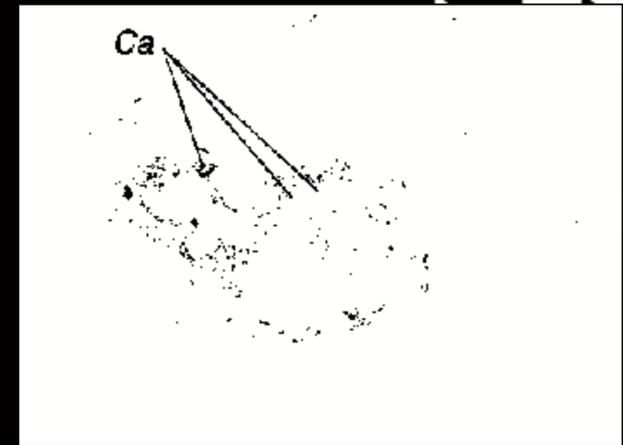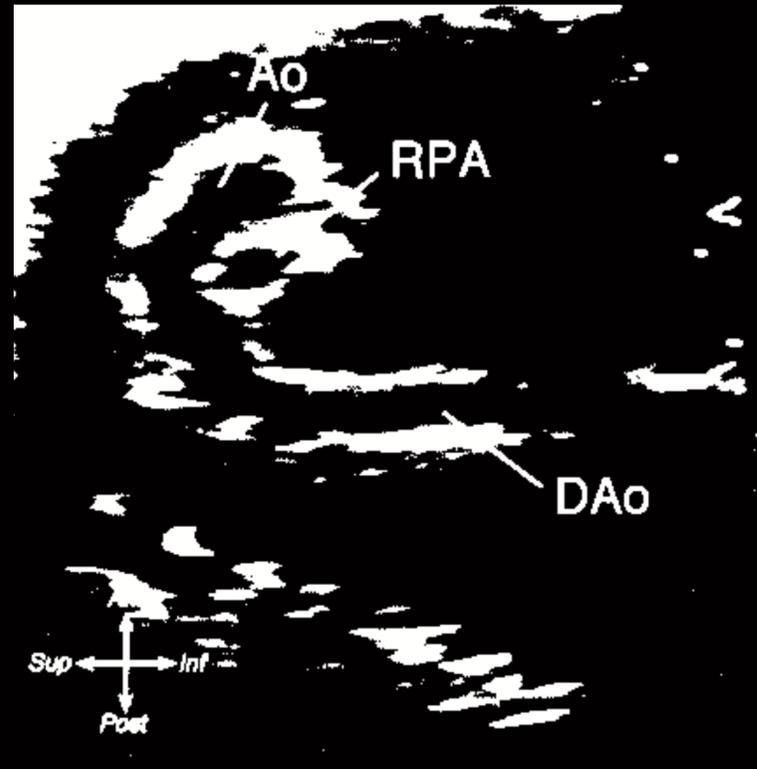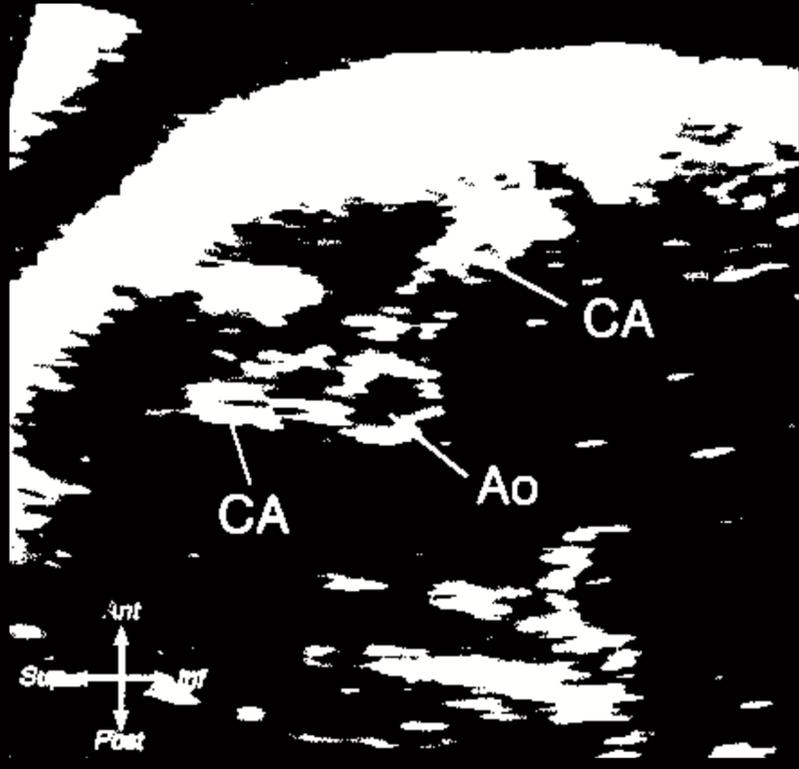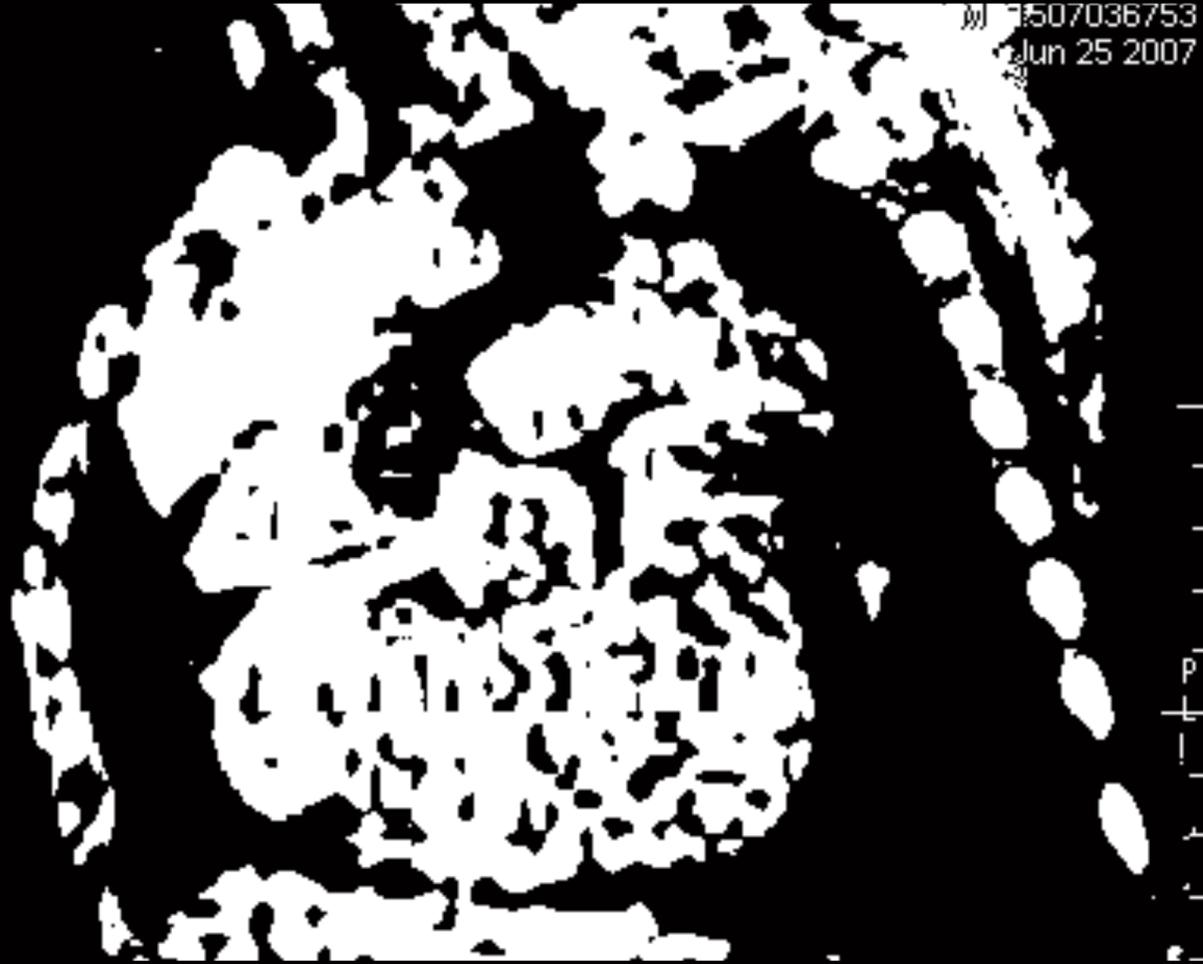
Acquired coronary anomalies

Kawasaki disease

Kawasaki disease : Key points 1

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.

Kawasaki disease : Key points 2

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 ≈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

No coronary artery changes

Mild, transient dilatation (resolves within 4-6 weeks)

Possible progression to a normal luminal dimension

Media

Intima

Aneurysm formation

Necrotizing arteritis

Further progression and ? possible interaction with atherosclerosis risk factors

Elastica interna

1. Subacute/chronic vasculitis
2. Luminal myofibroblastic proliferation
3. Laminar non-occlusive thrombosis

Adventitia

Destruction of intima, elastica interna, media and, variably, adventitia

Calcification

Occlusive thrombus formation

Complex stenosis

Ischemic heart disease

Myocardial infarction

Organization of thrombus and recanalization

Epicardial coronary artery (right) and epicardial vein (left) from a 19-month-old child who died 10 months after Kawasaki disease onset.

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.
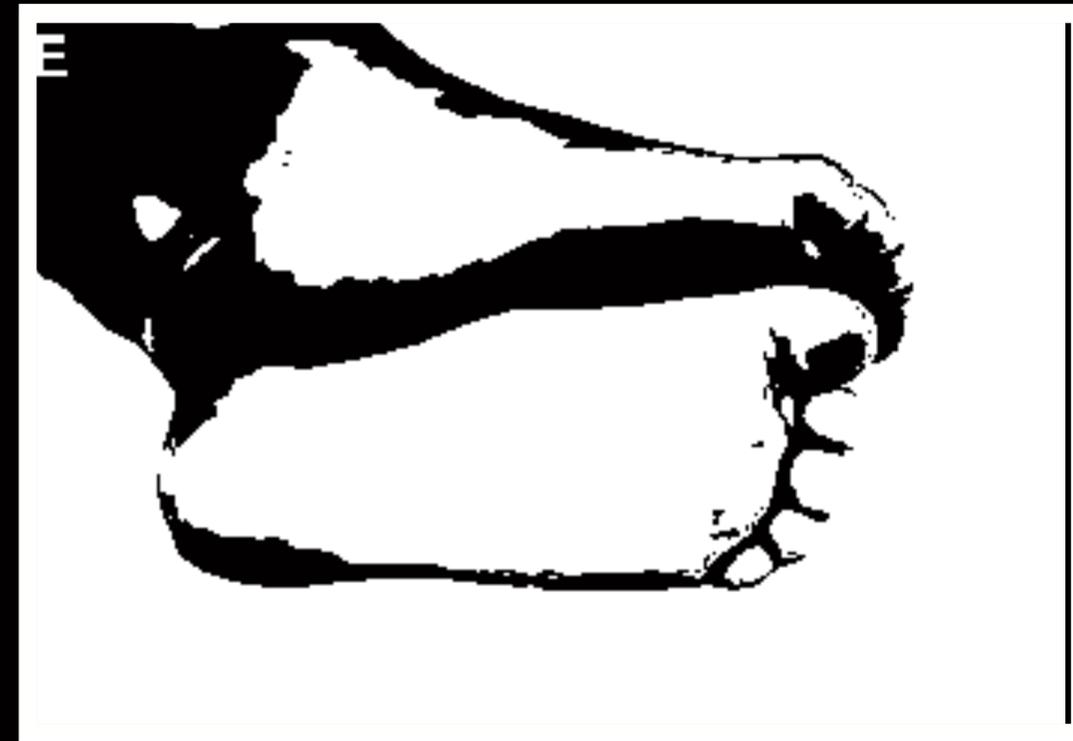
Clinical features of classic Kawasaki disease.

Clinical features of classic Kawasaki disease.

Fièvre
°C

39
38,5
38
37,5
37
36,5
36

Exanthème

Conjonctivite

Stomatite

Adénopathies

Atteintes des extrémités

Erythème
Œdème
Desquamation

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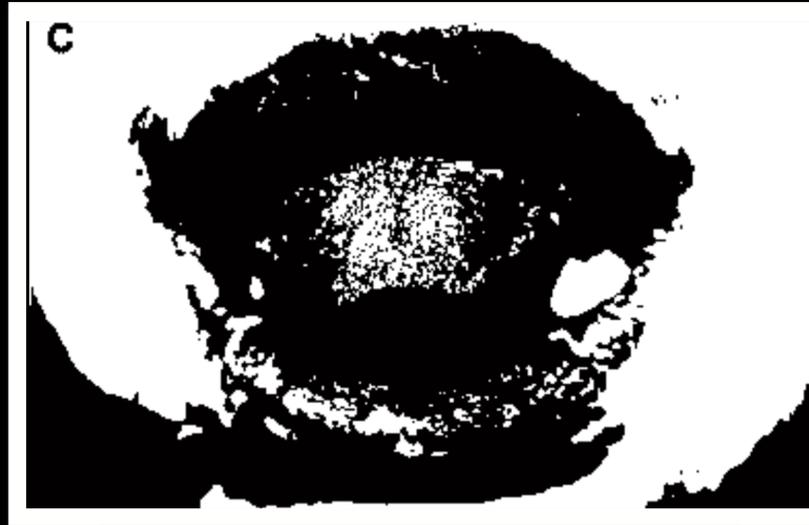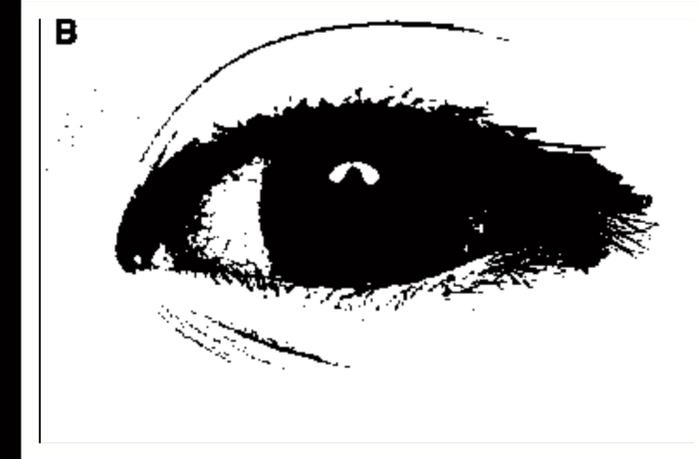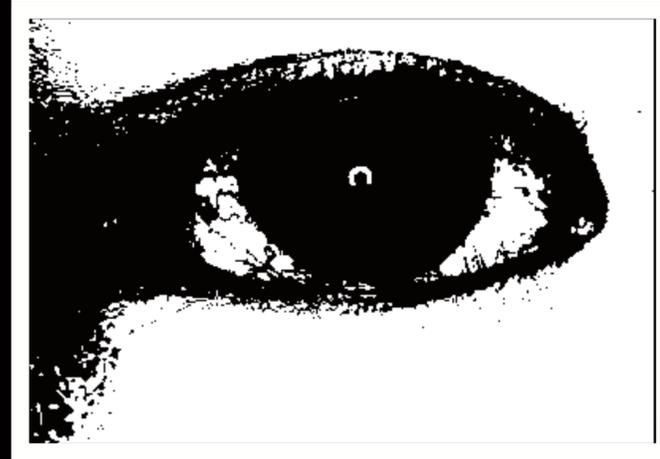
Jours (maladie)

Evaluation of suspected incomplete Kawasaki disease

Children with fever ≥5 days and 2 or 3 compatible clinical criteria[2] **OR** Infants with fever for ≥ 7 days without other explanation[3]

Assess Laboratory Tests

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

CRP≥3.0 mg/dL and/or ESR≥40 mm/hr

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

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

OR
Positive echocardiogram[4]

NO

YES

Treat[5]

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

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 Prevention of Thrombosis

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.

M3C

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Cardiomyopathies
Paris
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Collective ignorance is our motivation
Curiosity is our strength
Research is our path

Individual experience is the brake
Indifference is the weakness
Argument from authority is the threat