In 1928, Maude Abbott proposed that aortic dilatation and dissection in congenital heart disease were caused by medial structural abnormalities.

(Am Heart J 1928, 3:381).
An Early Step

Great arterial dilatation is common in congenital heart disease.

Dilatation is often out of proportion to hemodynamic and morphogenetic expectations.

Relatively little attention has been paid to the prevalence, degree and pathogenesis of the structural abnormalities of dilated great arterial walls in CHD.
BACKGROUND

Light and electron microscopic studies were performed in neonates through older adults on over 100 surgically excised biopsy specimens of the ascending aorta, paracocartation aorta, truncus arteriosus, and pulmonary trunk, supplemented by 20 necropsy specimens.
Controls

Aortic Root

• Positive controls:
  Marfan syndrome

• Negative controls:
  Trileaflet calcific AS; CABG; transplant donor

Pulmonary Trunk

• Negative controls:  CABG
Constituents of Arterial Media—Functional Roles

1) Smooth Muscle Cells – Contraction and relaxation (vasomotion).
2) Extracellular Matrix:
   a) Elastic Fibers – Phasic distension and recoil (pulsatile flow).
   b) Collagen and Ground Substance – Static strength (rigidity).
In 1930, Jakob Erdheim described “medioneecrosis aortae idiopathica cystica.” However, Erdheim’s medial necrosis is seldom encountered, and his “cystica” are noncystic medial faults.
Association of Aortic Valvular Disease and Cystic Medial Necrosis of the Ascending Aorta
Microscopic Analyses

• **Light Microscopy** — Superior for quantitative structural analysis of smooth muscle, elastic fibers, collagen, and ground substance.

• **Electron Microscopy** — Superior for qualitative sub-structural analysis of smooth muscle, elastic fibers and collagen.
Variables That Alter the Structure of Ascending Aortic Media

- Pregnancy
- Aging
- Systemic hypertension
- Mechanical stress
**Normal Gestational Changes in Aortic Media**

Fragmentation of elastic fibers
Decrease in ground substance
Hypertrophy/hyperplasia of smooth muscle cells

*It is not known whether these gestational changes normalize after pregnancy.*
Non-gravid

Aortic Media

Gravid
Aging

Fragmentation of aortic medial elastic fibers. Decrease in smooth muscle cells. Increase in collagen and ground substance, especially in the thoracic aorta.

Systemic Hypertension

Abnormalities of aortic medial elastin and collagen are significantly more prevalent than in normotensive subjects.

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Wall Stress

Longitudinal wall stress is an additional risk factor for ascending aortic dissection.
The Structural Integrity of Great Arterial Walls

Matrix is a dynamic structure that is central to the control of vascular remodeling, and that depends on the actions of proteolytic enzymes and their inhibitors.

If the structural integrity and physical properties of medial arterial matrix are not maintained, pulsatile mechanical stress will cause mural attenuation.
Principal Constituents of Arterial Media—Functional Roles

1) Smooth Muscle Cells – Contraction and relaxation (vasomotion).

2) Extracellular Matrix:
   a) Elastic Fibers – Phasic distension and recoil (pulsatile flow).
   b) Collagen and Ground Substance – Static strength (rigidity).
Extracellular Matrix

- **Elastic Fibers** — Synthesized by fibroblasts and smooth muscle cells. An elastin core is surrounded by a sheath of microfibrils composed of the glycoprotein fibrillin.
- **Collagen** — Thick connective tissue fibers.
- **Ground substance** — A hydrated gel composed of glycosaminoglycans (mucopolysaccharides), proteoglycans, and adhesive glycoproteins in which elastic fibers and collagen are imbedded.
Structural Integrity of Great Arterial Walls

The matrix is a dynamic structure that plays a central role in vascular remodeling that in turn depends on proteolytic enzymes and their inhibitors. If the structural integrity and physical properties of medial arterial matrix are not maintained, pulsatile mechanical stress will cause mural attenuation.
Matrix Metalloproteinases

The important role of matrix in maintaining arterial wall integrity. Do proteolytic enzymes (MMP’s) play pathogenetic roles in the medial abnormalities of dilated great arteries in congenital heart disease?
Matrix Metalloproteinases in Congenital Heart Disease

The UCLA Adult Congenital Heart Disease Center in collaboration with Dr Luyi Sen’s laboratory is characterizing protein expression levels of MMP’s utilizing quantitative western blot and zymographic analysis of surgically excised specimens of great arterial walls from the same spectrum of patients studied with light and electron microscopy.
Metallothionein

A metal-bonding protein that regulates metalloproteinases, and is upregulated in response to oxidative stress. Upregulation in the ascending aorta may play an important role in aneurysm formation above a bicuspid aortic valve.
Morphologic Grading System

Normal—Elastic fibers are closely packed in orderly parallel arrays.

Grade 1—Mild fragmentation of elastic fibers, mild increase in collagen.

Grade 2—Disruption and fragmentation of elastic fibers, loss of smooth muscle cells, greater increase in collagen.

Grade 3—Virtual loss of elastic fibers and smooth muscle cells. Appreciable increase in collagen and ground substance.
Light Microscopy

AORTA (EVG stain)

LOW POWER

HIGH POWER

NORMAL

GRADE 1
Light Microscopy contd.

E, G, a

GRADE 2

GRADE 3

Ahmanson/UCLA Adult Congenital Heart Disease Center
Light Microscopy

AORTA (Polychromatic stain)

A: NORMAL

B: GRADE 1

C: GRADE 2

D: GRADE 3
Aortic Root Areas of Interest

- Asc aorta
- ST junction
- Sinuses

Diagram showing:
- Annulus
- Sinus
- Septum
- LVOT (Left Ventricular Outflow Tract)
- AMVL
- Asc AO (Ascending Aorta)
The presence of a bicuspid aortic valve appears to indicate, at least in a portion of the cases in which it occurs, a tendency for spontaneous rupture.

Maude Abbott 1928
Abraham Lincoln
1863 photograph

Blurred left foot was a clue of the aortic regurgitation of Marfan syndrome
Marfan Syndrome

The Fibrillin-1 Protein

Fibrillin-1 is a modular protein encoded by the large (230-kb) \textit{FBN1} gene that contains 65 coding exons.
There is no disease more conducive to clinical humility than aneurysm of the aorta.

William Osler
Ascending Aortic Aneurysm

Pectus excavatum deformity

Main Pulmonary artery

Left atrium

Superior Vena Cava

Descending aorta

Main Pulmonary artery
Ascending aortic aneurysm

Distal ascending aorta

Cranial

Caudal

Right

Left

Distal ascending aorta
Turner Syndrome
Ascending Aortic Aneurysm
DeBakey, at age 97, underwent an operation that he pioneered---repair of an ascending aortic aneurysm.
The Bicuspid Aortic Valve

Aortic root dilatation
Medial structural abnormalities
Aortic dissection
Fibrilin-1 microfibrils tether smooth muscle cells to the elastin/collagen matrix

Deficient microfibrils result in smooth muscle cell detachment, matrix disruption and cell death

*Fedak et al, Circulation 2002*
Discrete Sub AS

Discrete Supravalve AS

The Aortic Root Is Not Dilated
Restrictive Ventricular Septal Defect

Age 6 Years

Ascending Aortic Dilatation

Ascending Aortic Media

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Fallot’s Tetralogy
Age 8 Years

Ascending Aortic Dilatation

Ascending Aortic Media

Ahmanson/UCLA Adult Congenital Heart Disease Center
Fallot’s Tetralogy
Ascending Aortic Dilatation
Fallot’s Tetralogy
Dilated Aortic Root/AR. Age 52 Years
Marfan

Bicuspid Aortic Valve

VSD

Fallot
*Sinus of Valsalva Aneurysm*

...the essential lesion is a defect in continuity of the media of the aortic root. *Mayo Clin Proc 1956*

...a developmental error involving differentiation of tissues at the base of the aorta. *Am Heart J 1960*
Coarctation of the Aorta
An Experiment of Nature
Coarctation of the Aorta

Para-coarctation Aorta
Para-coarctation Media
Coarctation of the Aorta

Resection With End-to-End Anastomosis

Patch Graft
Coarctation With Bicuspid Aortic Valve

In coarctation, a relatively rigid ascending aorta caused by increased collagen and decreased smooth muscle tends to persist after repair, and exerts an adverse effect on the coexisting medial abnormalities of a bicuspid aortic valve.
Coarctation

The Neonatal Ascending Aorta

Elastic properties of the ascending aorta are inherently abnormal in coarctation. This inborn fault remains unchanged after successful operation.

Vogt et al. Circulation June 2005
Fusion of the right and *non-coronary* cusps (R-N) is significantly associated with cuspal abnormalities (aortic stenosis and regurgitation).

Fusion of the *right and left* coronary cusps (R-L) is significantly associated with coarctation of the aorta.
D-TGA Arterial Switch
The Suture Line

Ascending Aorta

Ascending Aortic Media

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Arterial Switch

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Neonatal Ductal Aneurysm

Ductal Aneurysm Media
Neonatal Truncus Arteriosus

The Truncus

MPA

Tr.

The Truncal Media
Eisenmenger Truncus Arteriosus
Age 52 Years
The Pulmonary Trunk

Mobile Pulmonary Valve Stenosis

Dysplastic Pulmonary Valve Stenosis

Dilated

Non-dilated
Pulmonary Valve Stenosis

PT

SVC

Asc Ao

PT

DAo

Pulmonary Trunk Media
Ostium Primum ASD

Left-to-Right Shunt

Pulmonary Trunk Media
Fallot’s Tetralogy
Absent Pulmonary Valve
Severe Pulmonary Regurgitation

Aneurysmal Proximal Pulmonary Arteries
Fallot’s Tetralogy
Absent Pulmonary Valve

Severe PR

Media
Pulmonary Trunk
Fallot’s Tetralogy Transannular Patch
Severe Pulmonary Regurgitation

Mild Pulmonary Artery Dilatation
Eisenmenger ASD
Aneurysmal Pulmonary Trunk
Eisenmenger VSD
Aneurysmal Pulmonary Trunk
Fallot’s Tetralogy, Potts Shunt, PVD
Ruptured Pulmonary Trunk
CONCLUSIONS

Medial structural abnormalities of great arterial smooth muscle, elastic fibers, collagen and ground substance are present in a wide variety of congenital heart diseases from neonates to older adults.

**Ascending Aortic Media**

Abnormalities predispose to dilatation, aneurysm formation and rupture, and are potential surgical risks.

*Ahmanson/UCLA Adult Congenital Heart Disease Center*
Pulmonary Trunk

In patients with mobile pulmonary valve stenosis and Fallot’s tetralogy with absent pulmonary valve, medial abnormalities of the pulmonary trunk predispose to dilatation and aneurysm formation. Hypertensive proximal pulmonary arteries may be aneurysmal and may rupture or thrombose.
PIVOTAL QUESTIONS

1) Are great arterial medial abnormalities in congenital heart disease inherent or acquired?

2) Does congenital heart disease play an etiologic or facilitating role?

3) If the medial abnormalities are in part inherent, to what extent are they genetically determined?
In 1928, Maude Abbott proposed that aortic dilatation and dissection in congenital heart disease were caused by medial structural abnormalities.

(Am Heart J 1928)
“The presence of a bicuspid aortic valve appears to indicate, at least in a portion of the cases in which it occurs, a tendency for spontaneous rupture.”

Maude Abbott 1928
Inadequate fibrillin-1 expression during valvulogenesis disrupts normal aortic cusp formation, and can result in a bicuspid aortic valve.

Inadequate fibrillin-1 expression in the contiguous ascending aortic media results in mural attenuation, dilation and dissection.
Metallothionein

This metal binding protein may regulate the response of aortic smooth muscle cells to oxidative stress, to MMP expression, and to tissue homeostasis of aortic extracellular matrix.

In the presence of a bicuspid aortic valve, there is a genetically determined defect in the cellular microenvironment of the ascending aortic wall characterized in part by decreased expression of metallothionein.
Fibrillin-1 microfibrils tether smooth muscle cells to the elastin/collagen matrix

Deficient microfibrils result in smooth muscle cell detachment, matrix disruption and cell death

Fedak et al, Circulation 2002;106:900-904
The Bicuspid Aortic Valve

Ascending Aortic dilatation.
Medial structural abnormalities.
Aortic dissection.
Restrictive Ventricular Septal Defect
Age 6 Years

Ascending Aortic Dilatation

Ascending Aortic Media
Fallot’s Tetralogy
Age 8 Years

Ascending Aortic Dilatation

Ascending Aortic Media
Fallot’s Tetralogy
Dilated Aortic Root/AR Age 52 Years
Coarctation of the Aorta
An Experiment of Nature
Coarctation of the Aorta

Para-coarctation Aorta

Para-coarctation Media
Neonatal Truncus Arteriosus

The Truncus

The Truncal Media
Eisenmenger VSD Age 42 Years

Aortic Dissection

Aortic Media

Ahmanson/UCLA Adult Congenital Heart Disease Center
Conclusions

Abnormalities of great arterial medial smooth muscle, elastin, collagen and ground substance occur in a wide variety of congenital heart diseases from neonates to older adults.

These ascending aortic medial abnormalities predispose to dilatation, aneurysm formation and rupture, and are potential cardiac surgical risks.
Pivotal Questions

1) Are great arterial medial abnormalities in congenital heart disease intrinsic or acquired?

2) Does congenital heart disease play an etiologic or a facilitating role?

3) If the medial abnormalities are intrinsic, to what extent are they genetically determined?
A Variation on the theme.

From great arterial walls to coronary arterial walls.
Coronary Arterial Walls in Cyanotic Congenital Heart Disease

Dilatation Exceeds the Response from Endothelial Vasodilators

Gross Morphology
Dilated tortuous extra-mural coronary arteries.

Histology
Loss of medial smooth muscle.
Increase in medial collagen.
Duplication of the internal elastic lamina.
1 = LOSS OF MEDIAL SMCs; 2 = INCREASED MEDIAL COLLAGEN
3 = DUPLICATION OF IEL; 4 = FIBROMUSCULAR INTIMAL HYPERPLASIA
Thank You
Luetic Aortic Eneurysm
PO Fallot Severe PR
Aneurysmal Dilatation
Proximal Pulmonary Arteries
Matrix Metalloproteinases

A group of zinc dependent proteolytic enzymes that function in the resorption of extracellular matrices. Nine MMP’s have been identified, cloned and sequenced. A family of naturally occurring inhibitors coexist with MMP’s.
Luetic fusiform aneurysm of ascending aorta