

HHT and Aging

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Disclosures

- Conflicts of interest/commercial endorsements: None



Case Presentation

- 90 year old female (now)
 - Age 5, onset of mild nose bleeding
 - Never severe, or interfering with activities
 - Essentially stopped having them as an adult
 - Grand-daughter diagnosed with HHT
 - Lung AVM found in pregnancy
 - Diagnosed with HHT at age 85
 - No brain or lung AVM
 - Deep vein thrombosis
 - Placed on Xarelto (blood thinner)

Case Presentation – cont'd

- New onset bleeding after starting Xarelto
 - Nose bleeding, but rare and mild (ESS 0.72)
 - Significant GI bleeding (telangiectasias seen)
 - Required transfusions and IV iron
- Stopped Xarelto
 - Bleeding stopped, no further requirement for transfusion/IV iron
- No nose bleeds in the past year, not on iron
 - ESS is 0
 - Hemoglobin 14.9 g/dL (Normal 12.6-15.9)
 - Ferritin 45 ng/mL (Normal 18-340)

Life Expectancy in HHT

- Without screening for AVMs
 - Median (IQ range)
 - Non-HHT spouse: 76.6 years (68.5-83.2)
 - HHT: 73.3 years (63.6-81.7)
 - Endoglin: 69.5 years (59.3-81.4) *
 - ACVRL1: 76.0 years (67.1-82.9)

de Gussem et al. Orphanet Journal of Rare Diseases, 2016

Lung and Brain AVM are more likely with Endoglin mutation

TABLE III. Organ Involvement in Patients With HHT1 or HHT2

	HHT1 (%)	HHT2 (%)	P-value
Intrapulmonary shunt ^a	59.0 (36/61)	28.9 (13/45)	0.002
Cerebral AVM	16.4 (10/61)	2.0 (1/50)	0.012
Spinal cord AVM	0.0 (0/61)	4.0 (2/50)	NS
Hepatic involvement	1.7 (1/59)	27.7 (13/47)	<0.001 ^b

NS, non-significant.

^aEvidence of intrapulmonary shunt by chest CT, angiography, and/or contrast echocardiogram.

^bFisher's exact test was used.

HHT1 = Endoglin

Bayrak-Toydemir et al., Am J Med Genet 140A (2006)

Aging in general

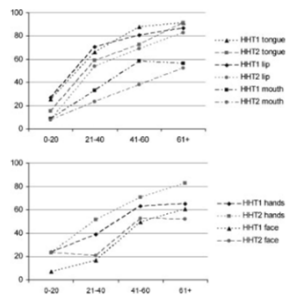
Rank ¹	Cause of death (based on the ICD-10, 2004)	Number	Percent of total deaths
...	All causes	2,437,163	100.0
1	Diseases of heart (I00-I09, I11, I13, I20-I51)	599,413	24.6
2	Malignant neoplasms (C00-C97)	567,628	23.3
3	Chronic lower respiratory diseases (J40-J47)	137,353	5.6
4	Cerebrovascular diseases (I60-I69)	128,842	5.3
5	Accidents (unintentional injuries) (V01-X59, Y85-Y86)	118,021	4.8
6	Alzheimer's disease (G30)	79,003	3.2
7	Diabetes mellitus (E10-E14)	68,705	2.8
8	Influenza and pneumonia (J09-J18)	53,692	2.2
9	Nephritis, nephrotic syndrome and nephrosis (N00-N07, N17-N19, N25-N27)	48,935	2.0
10	Intentional self-harm (suicide) (*U03, X80-X84, Y87.0)	36,909	1.5

Top 10 causes of death: 2009

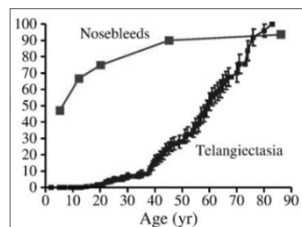
Aging with HHT



Telangiectasias increase with age



Nose bleeding increases with age



Heart failure increases with age

- Last 193 adults at Utah HHT Center:
 - 24% have markers of heart failure
- By age:
 - 20-40 years old: 0%
 - 40-55 years old: 7%
 - 55-70 years old: 32%
 - Over 70 years old: 74%

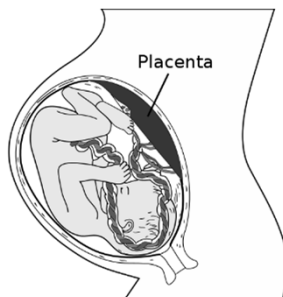
HHT doesn't directly affect the heart

- Common targets:
 - Mucus membranes
 - Skin
 - Brain
 - Lung
 - Liver
- Heart pays a price due to other organ involvement
- Treatment of Heart Disease is complicated by HHT

Impact of Systemic Shunts

- Consider the impact of having a large vascular shunt in an abdominal organ.
- Over time the organ demands more and more blood flow, eventually increasing the total work of the heart by 50%
- Now, everything is a greater effort
 - Walking feels like jogging
 - Jogging feels like running
 - Running is almost impossible
- Because of high flow, fluid retention starts to happen throughout the body
 - Swollen ankles, shortness of breath

Common High Volume "Vascular Malformation"

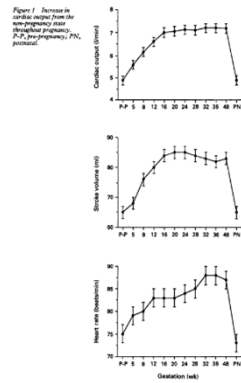


Cardiac Output in normal singleton pregnancy

Cardiac output increases 45%

30% more volume per beat

16% more beats per minute



Hunter & Robson, Br. Heart J 1992



Liver Shunting in HHT



Liver involvement in HHT

- Vascular malformations (VM) of the liver are common
 - 67 to 74% by CT scan
- Symptoms from liver VM are rare
 - About 10% of patients

Buscarini et al. *Liver Int.* 26:1040-6 (2006)

Blood Vessels & the Liver

- Intersection of three sets of blood vessels
 - Hepatic artery (high pressure blood from heart)
 - Portal vein (high nutrient content draining from gut)
 - Hepatic vein (drains the leftovers of both to the heart)
- HHT is a disease of disordered blood vessel connections
 - Hepatic artery to hepatic vein
 - Hepatic artery to portal vein
 - Portal vein to hepatic vein

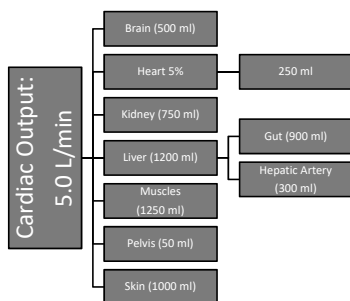
Hepatic Artery to Hepatic Vein Shunts



The Math

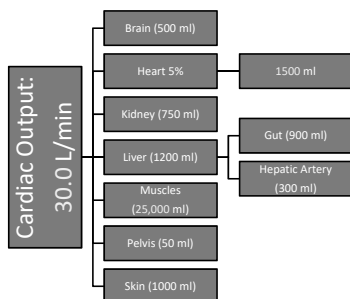
- Liver statistics (the normal liver)
 - 2% of the body's weight
 - 25% of the body's blood flow
 - 6-8% directly from hepatic artery
 - 17-19% portal vein - after first supplying the gut
- There is a lot of potential for extra blood flow through that hepatic artery
- Heart maximum capacity:
 - About 30 L/min (if well trained)

Resting Blood Flow*

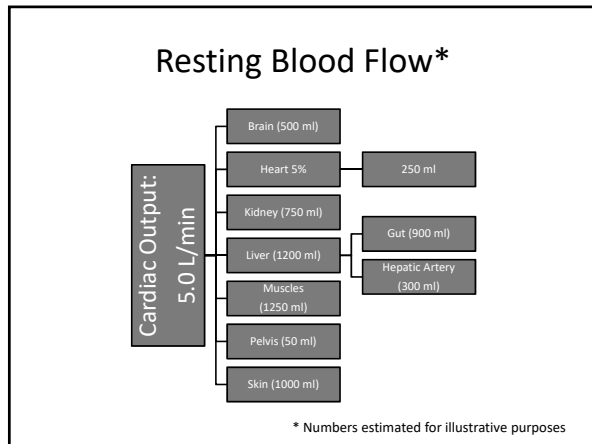


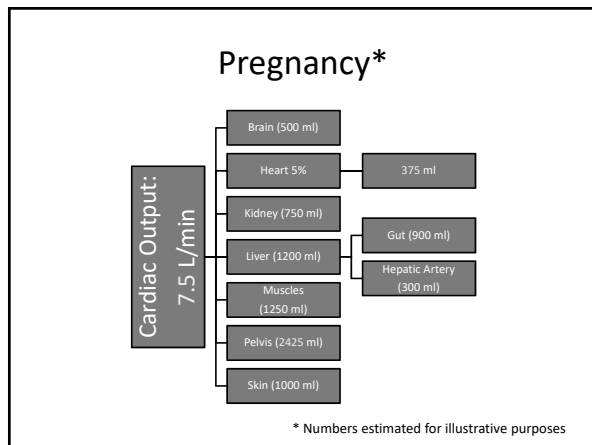
* Numbers estimated for illustrative purposes

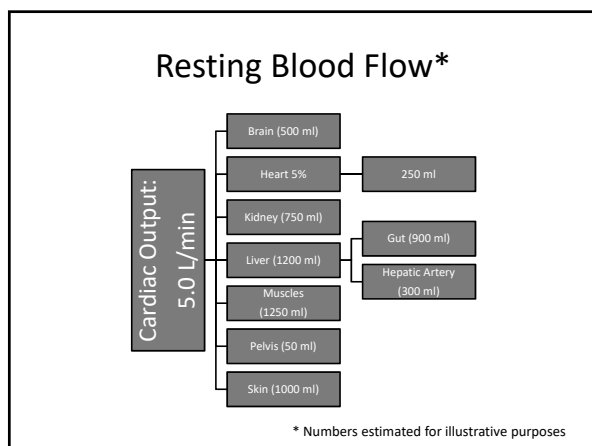
Running a Marathon*

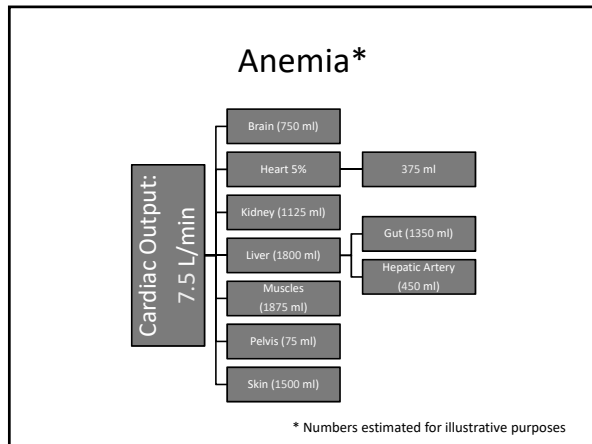


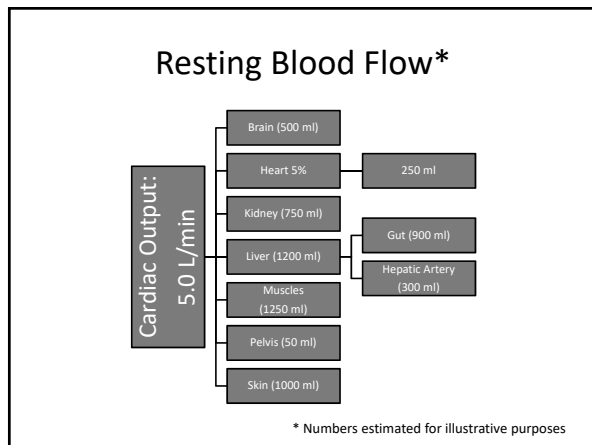
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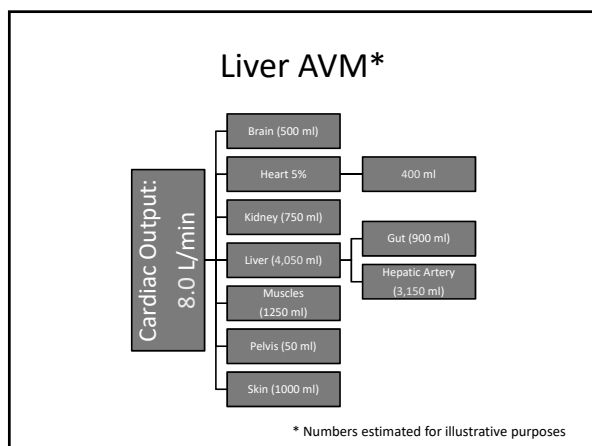


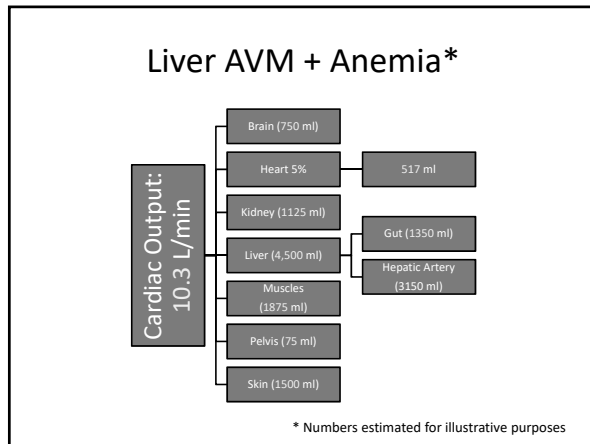












Chronic High Output

- Imagine being 9 months pregnant forever...
- Heart loses efficiency
 - High output continues
 - ...but cardiac filling pressure rises (congestion)
 - Increased left atrial pressure: shortness of breath, PHTN
 - Increased right atrial pressure: leg edema, ascites, effusions
- HIGH OUTPUT HEART FAILURE

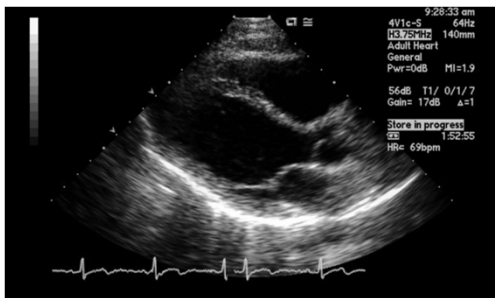
Heart Failure

- Heart unable to meet the body's demands
- Systolic vs. Diastolic Heart Failure
 - Systole: contraction phase
 - Diastole: relaxation phase

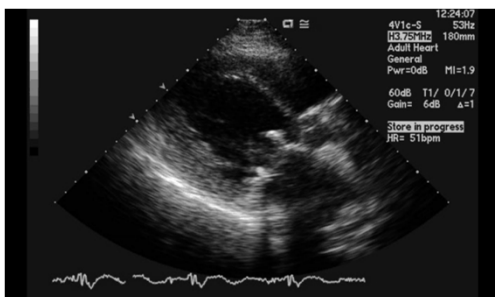
Systolic Heart Failure

- Weak heart phenotype
 - Low ejection fraction
- Causes
 - Ischemic heart disease/coronary disease
 - Dilated cardiomyopathy/genetic muscle weakness
 - Toxic cardiomyopathy/chemotherapy, alcohol
 - Other (thyroid disease, infiltrative disease...)

Normal Heart



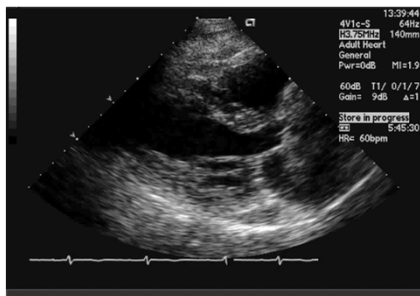
Systolic Heart Failure



Diastolic Heart Failure

- Stiff heart phenotype
- Heart can't relax
- Heart still looks strong
 - Normal ejection fraction
- Causes:
 - Hypertension
 - Diabetes
 - Amyloidosis
 - Other...

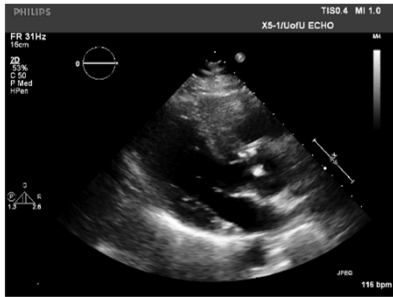
Diastolic Heart Failure



High Output Heart Failure

- Heart can't keep up with high demands
 - Heart is intrinsically normal
- Heart looks better than normal
 - High ejection fraction
 - (Often overlooked)
- Causes (rare):
 - Liver AVM
 - Severe, chronic anemia
 - Untreated hyperthyroidism
 - Beriberi (thiamine deficiency)
 - Paget's disease of bone

High Output Heart Failure



USA Heart Failure Epidemic

- Estimated 5.1 million patients in USA
 - (almost 2% of population)
- Systolic Heart Failure (60%)
 - 3 million patients
- Diastolic Heart Failure (40%)
 - 2 million patients
- High Output Heart Failure (<1%)
 - Unknown number...
 - In HHT, assume...
 - 30,000 USA patients with HHT (1 in 10,000 people)
 - 20,000 with liver AVM (67%)
 - 2000 with symptoms (10%)
 - ~ 1 in every 2,500 heart failure patients

Heart Failure in HHT

- Numbers previously unreported
- Back to our assumptions:
 - High output heart failure:
 - Estimate: 2000 patients in USA
 - Other forms of heart failure in 2%
 - Another 600 patients expected
 - If HHT predisposes... even higher

Utah Experience

- All adult patients seen from January 2015 through February 2019 (195 patients)
 - All patients screened with BNP and echocardiogram
 - Cardiac catheterization usually performed with suspected heart failure
 - 46/195 had BNP greater than 100 (24%)
 - Of those, 17 had high cardiac index (>4.0 L/min/m²)
 - 28 had normal index (2.4-4.0)
 - 1 had low index (patient with severe PAH)

Heart Failure Etiologies

- Chronic diastolic heart failure (HFpEF)
 - 27/195 (14%) had EF $\geq 50\%$ with normal index
- Chronic systolic heart failure (HFrEF)
 - 1/195 (0.5%) had EF $< 50\%$ with normal index
- High output heart failure (HOHF)
 - 17/195 (9% incidence) had high index
 - ACVRL 10% - Endoglin 4%
- Cor pulmonale due to PAH
 - 1/195 (0.5% incidence)

Pulmonary Hypertension

- 49 year old female, short of breath
- Cardiac catheterization
 - Pressures (with normal values)
 - Systemic veins 13 (5 mmHg is normal)
 - Pulmonary artery 79/17 (30/10 mmHg is normal)
 - Pulmonary veins 20 (12 mmHg is normal)
 - Aorta 80/40 (120/70 is normal)
 - Cardiac output
 - 11.6 L/min (5.4 L/min is normal)
 - Resistance
 - Pulmonary 1.30 units (0.3-1.7 is normal)
 - Systemic 3.80 units (10-20 is normal)

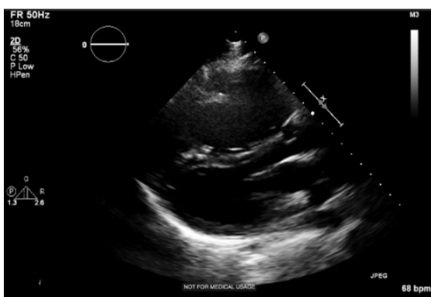
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Pulmonary Hypertension due to High Output Heart Failure

- All of the cardiac output is sent to the lungs for oxygen
- There is only so much room in the lung blood vessels
- When a great deal more blood is sent to the lungs than normal, the pressure will rise
 - Like turning a hose on full blast...
- The lungs can start to “fight back” and increase their resistance to decrease the flow

High Output Heart Failure (HHT)



Same Patient, 5 months later Pulmonary HTN from chronic high flow

- 49 year old female, short of breath
- Cardiac catheterization
 - Pressures (with normal values)
 - Systemic veins 16 (5 mmHg is normal)
 - Pulmonary artery 57/25 (30/10 mmHg is normal)
 - Pulmonary veins 13 (12 mmHg is normal)
 - Aorta 72/43 (120/70 is normal)
 - Cardiac output
 - 9.15 L/min (5.4 L/min is normal)
 - Resistance
 - Pulmonary 2.51 units (0.3-1.7 is normal)
 - Systemic 4.59 units (10-20 is normal)

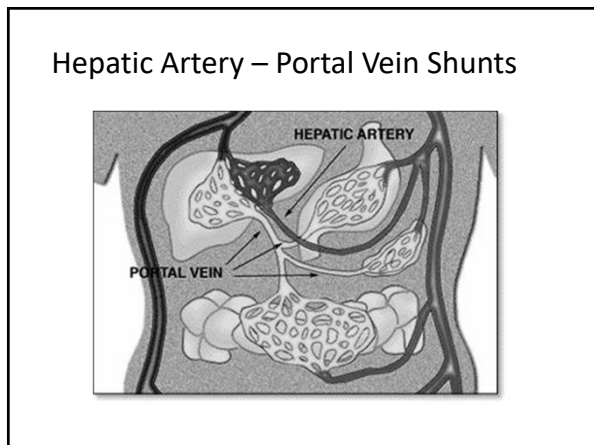
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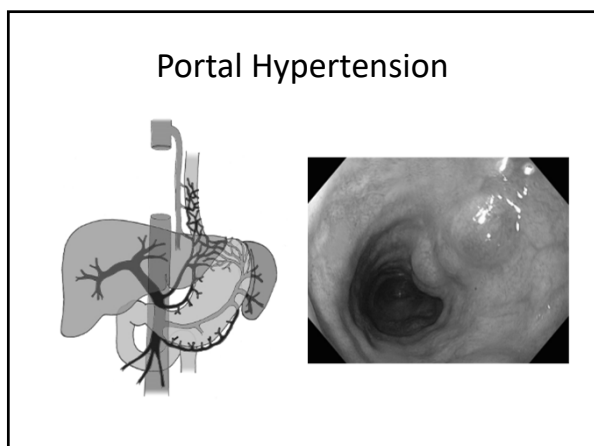
- Response to chronic high flow
- Rarely develops on its own for apparently no good reason
 - When it happens, almost always in ACVRL1

Pulmonary HTN from vascular changes High Resistance

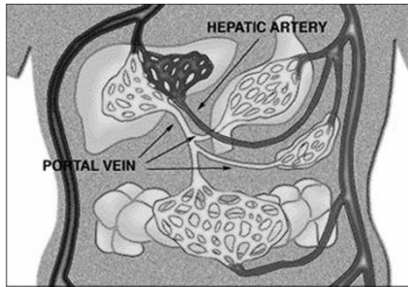
- 45 year old female, short of breath
- Cardiac catheterization
 - Pressures (with normal values)
 - Systemic veins 16 (5 mmHg is normal)
 - Pulmonary artery 93/47 (30/10 mmHg is normal)
 - Pulmonary veins 10 (12 mmHg is normal)
 - Aorta 118/85 (120/70 is normal)
 - Cardiac output
 - 3.07 L/min (4.7 L/min is normal)
 - Resistance
 - Pulmonary 16.6 units (0.3-1.7 is normal)
 - Systemic 26.4 units (10-20 is normal)







Portal Vein – Hepatic Vein Shunts



Case Presentation

- 63 year old male
 - HHT Type 2
 - Moderate epistaxis, chronic anemia
 - No brain or lung AVM
 - Liver AVM
 - Diffuse arterial enhancement, HA: 14 mm
 - No ascites or splenomegaly
 - Normal Alk Phos, AST, ALT
 - High output heart failure, CI: 4.6, PCW: 21, BNP: 421
 - Treated with bevacizumab

January 2015

- Severe nose bleed, controlled by self-packing
- Next morning: unarousable and non-responsive
 - Ammonia 175 $\mu\text{mol/L}$ (normal 9-30 $\mu\text{mol/L}$)
 - Hydration, lactulose (powerful laxative)
- Slow recovery, confusion x 48 hours
 - Maintained on chronic lactulose

Hypothesis:

- Hepatic encephalopathy (including high ammonia level) is a manifestation of liver AVM in HHT
- Included serum ammonia in routine screening of adults

Results:

- Total Patients: 193
 - Age: 52.0 (Range: 20.5-89.2)
 - Sex: 59% Female
 - Genotype:
 - ACVRL1: 130 (67%)
 - Endoglin: 52 (27%)
 - SMAD4: 1 (0.5%)
 - Negative: 2 (1%)
 - Unknown: 8 (4%)

Patients with elevated ammonia

- Total 18/193 patients
 - Genotype:
 - ACVRL1: 17 patients (13.1% incidence)
 - Endoglin: 0 patients
 - SMAD4: 0 patients
 - Negative: 1 patient
 - Unknown: 0 patients

Manifestations of liver AVM

- Liver AVM manifestations of 18 patients with high ammonia:
 - Cardiac (hepatic artery to hepatic vein shunt phenotype):
 - High output heart failure: 8/18 patients
 - All forms of heart failure: 13/18
 - Liver (Abnormal liver enzymes and/or function):
 - High alkaline phosphatase (>126): 6/18
 - High bilirubin (> 1.4): 4/18
 - High AST (>40): 2/18
 - High ALT (>60): None

Manifestations of liver AVM

- Patients with no other indicator of liver AVM:
 - 3 patients
 - 53 y.o. male, ACVRL1, severe epistaxis
 - 69 y.o. male, ACVRL1, moderate epistaxis
 - 59 y.o. male, Negative genotype, mild epistaxis

Symptoms of high ammonia

- Not all patients were symptomatic
- Occasionally clinically important
 - 76 y.o. female with episodic "zoning out"
 - 42 y.o. female schoolteacher
 - trouble remembering lesson plans
 - 81 y.o. male, thought to have mild dementia
 - 3 patients admitted with hepatic encephalopathy

Where does ammonia come from?

- Ammonia is produced by gut bacteria
 - Bacteria live off of our waste products
 - We absorb their waste products
 - Protein in the colon is an important source of nitrogen for NH_3
 - Concern that blood delivery to colon is a key driver
- Liver AVM, underlying vascular malformation
 - Hypothesize that portal vein to hepatic vein malformation lets toxins drain through the liver without processing
 - “Porto-systemic shunt”



HHT complicating
common heart disease

HHT Complicating Other Heart Disease

- Heart disease is common
 - Leading cause of death in men and women
 - Affects 35% in USA (84 million people)
- Mortality rates are dropping
 - Over 10% decrease in deaths from 2000 – 2010
 - Better prevention (statins)
 - Better treatment (reliant on blood thinners)

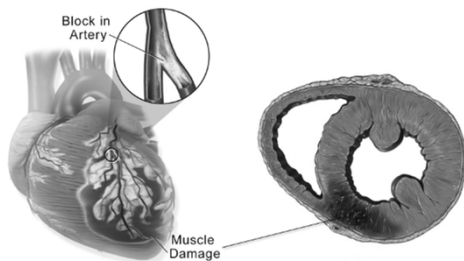
Can we thin the blood in HHT?

- We can always thin the blood, but does it make sense?
- Bleeding will increase (probably)
 - Not everyone bleeds worse, but most do
- Do the risks outweigh the benefits?
 - The more dangerous the condition, and the more effective the treatment, the more it makes sense to thin the blood

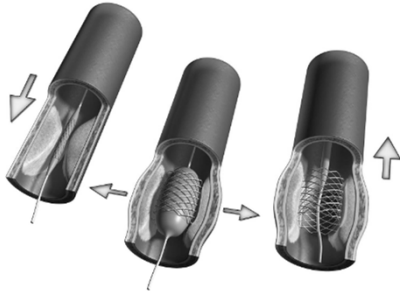
Can we decrease the risk of bleeding?

- Nose bleeds
 - Laser therapy
 - Medical therapy
 - Young's procedure

Myocardial Infarction



Myocardial Infarction



A stent can open the artery – but now requires blood thinners to avoid new clot

Risk/Benefit Decision:

- Heart attack
 - Risk of death in 30 days:
 - Untreated: 13%
 - Thrombolytic with Aspirin: 8%
 - Early stent: 5.3%
 - Most patients with HHT should receive these treatments
 - Can give iron/transfusions/nasal packing, etc. to get patients through the bleeding

Atrial Fibrillation

- Common condition
 - 10% of all people over 80 years old
 - Common in heart failure
- Major cause of cardioembolic stroke
 - Key role of left atrial appendage, location of thrombus
 - Consider CHADS-VASc risk factors for stroke
 - Prior stroke, age over 65 or 75, heart failure, high blood pressure, diabetes, female, vascular disease
 - Effect of anticoagulation
 - Oral anticoagulants (warfarin, apixaban, rivaroxaban, etc)
 - prevent ~2/3 of strokes
 - Aspirin:
 - Only prevents 1/3 of strokes

Risk/Benefit Decision:

- Atrial Fibrillation and stroke risk:
 - CHADS-VASc stroke risk factors:
 - CHF, HTN, age > 65, diabetes, prior stroke/TIA (2 points) vascular disease, age > 75, female
 - Number of risk factors and annual stroke rate:

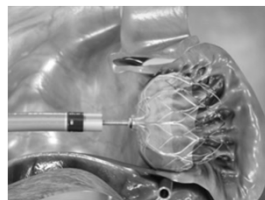
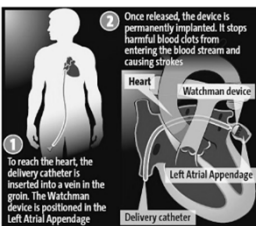
RF:	Stroke:	Stroke/TIA/systemic embolism:
0:	0.2%	0.3%
1:	0.6%	0.9%
2:	2.2%	2.9%
3:	3.2%	4.6%
4:	4.8%	6.7%
5:	7.2%	10.0%
6:	9.7%	13.6%
7:	11.2%	15.7%
8:	10.8%	15.2%
9:	12.2%	17.4%
 - Bleeding risk with Warfarin (outside of HHT): 2-3%/year
 - Where is a reasonable threshold for therapy? Patient specific answer...

Other options in Atrial Fibrillation



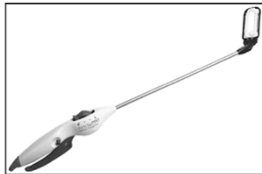
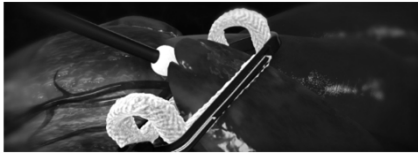
- Block off the Left Atrial Appendage – source of clot
 - Watchman device
 - Surgical AtriClip (video assisted thoracoscopy)

Watchman Device



Coumadin level protection with baby aspirin

Surgical AtriClip



Take Home Points

- Risk of early death from lung & brain AVM
 - Mortality otherwise may be unchanged
- Telangiectasias progress with age
 - Nose bleeding
 - Gastrointestinal bleeding
 - Liver AVM

Take Home Points

- HHT doesn't affect the heart directly
- HHT commonly affects the liver, but isn't usually symptomatic
- The most common HHT Liver complication is heart failure
- The heart failure of HHT is unusual
- HHT complicates management of common heart disease
- HHT patients should be managed at experienced centers to have the best outcomes
