



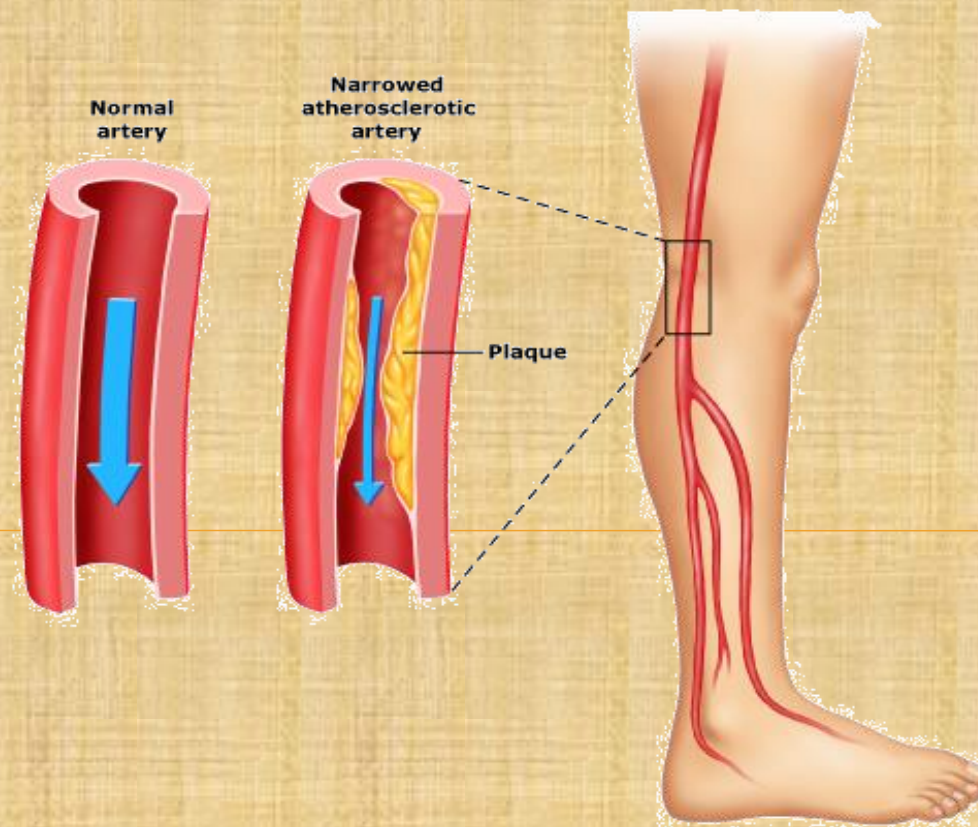
# **RELATION BETWEEN LOW SERUM TESTOSTERONE LEVEL AND PERIPHERAL ARTERIAL DISEASE IN MEN AND CLINICAL EVALUATION OF EFFECT OF TESTOSTERONE ADMINISTRATION.**

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# PERIPHERAL VASCULAR DISEASE

## ACUTE & CHRONIC LIMB ISCHEMIA



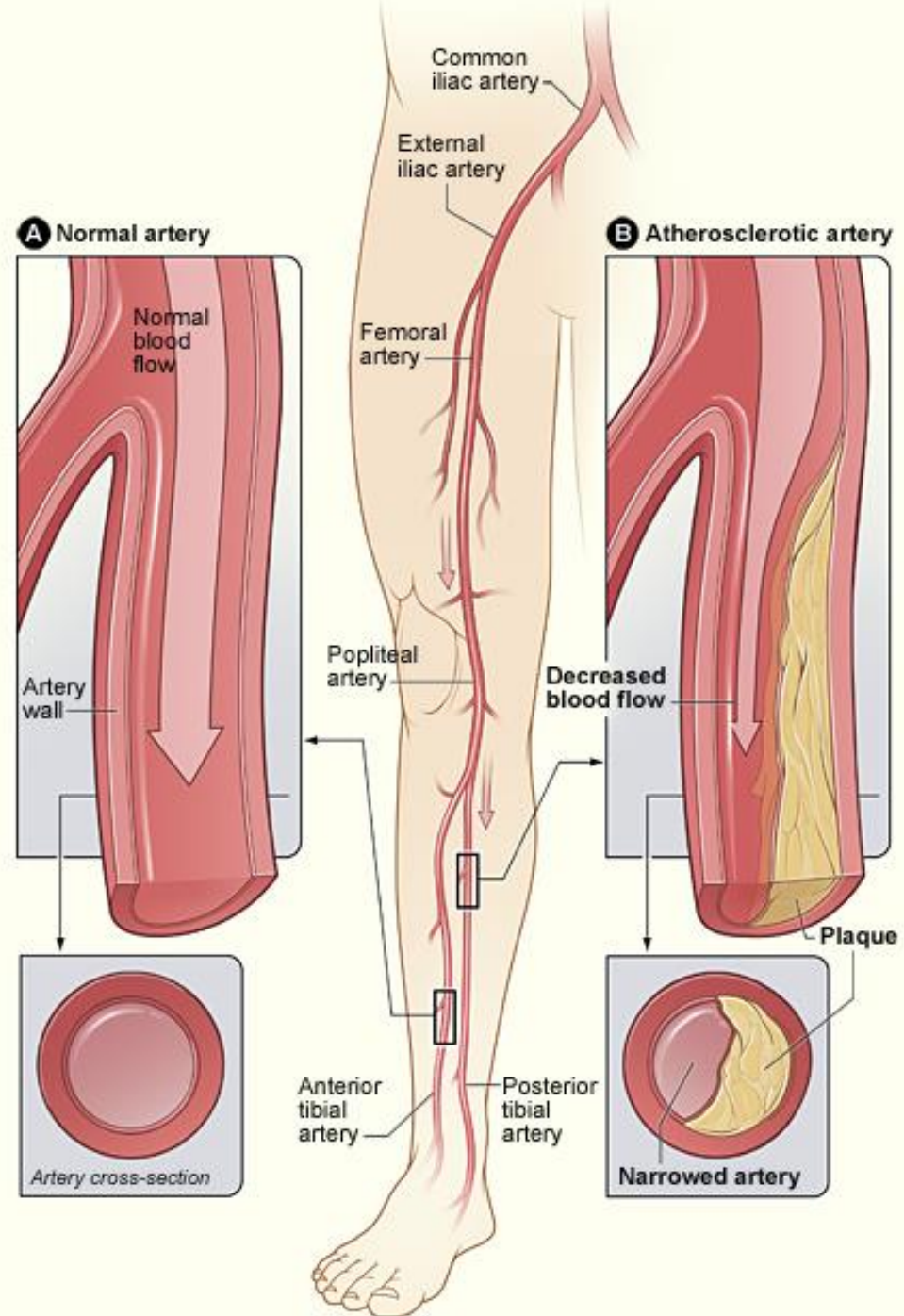
# WHAT IS PVD?

## Definition:


- Also known as PAD or PAOD.
- Occlusive disease of the arteries of the lower extremity.
- Most common cause:
  - Atherothrombosis
  - Others: arteritis, aneurysm + embolism.
- Has both ACUTE and CHRONIC Px

## Pathophysiology:

- Arterial narrowing → Decreased blood flow = Pain
- Pain results from an imbalance between supply and demand of blood flow that fails to satisfy ongoing metabolic requirements.



# THE FACTS:

- 
- 1. The prevalence: >55 years is 10%–25%**
  - 2. 70%–80% of affected individuals are asymptomatic**
  - 3. Pt's with PVD alone have the same relative risk of death from cardiovascular causes as those CAD or CVD**
- 
- 1. PVD pt's = 4X more likely to die within 10 years than pt's without the disease.**
  - 2. The ankle–brachial pressure index (ABPI) is a simple, non-invasive bedside tool for diagnosing PAD — an ABPI <0.9 = diagnostic for PAD**
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- 1. Patients with PAD require medical management to prevent future coronary and cerebral vascular events.**
- 
- 1. Prognosis at 1 yr in patient's with Critical Limb Ischemia (rest pain):**
    - Alive with two limbs — 50%**
    - Amputation — 25%**
    - Cardiovascular mortality 25%**

# RISK FACTORS:

## Typical Patient:

- **Smoker (2.5-3x)**
- **Diabetic (3-4x)**
- **Hypertension**
- **Hx of Hypercholesterolemia/AF/IHD/CVA**



- **Age  $\geq$  70 years.**
- **Age 50 - 69 years with a history of smoking or diabetes.**
- **Age 40 - 49 with diabetes and at least one other risk factor for atherosclerosis.**
- **Leg symptoms suggestive of claudication with exertion or ischemic pain at rest.**
- **Abnormal lower extremity pulse examination.**
- **Known atherosclerosis at other sites (eg, coronary, carotid, or renal artery disease).**

# CHRONIC PVD HISTORY:

## 1. INTERMITTENT CLAUDICATION

- Derived from the Latin word ‘to limp’
- “Reproducible pain on exercise which is relieved by rest”
- Pain can also be reproduced by elevating the leg
- “my legs get sore at night and feel better when I hang them over the edge of the bed”

## 2. Other Symptom/Signs:


- A burning or aching pain in the feet (especially at night)
- Cold skin/feet
- Increased occurrence of infection
- Non-healing Ulcers
- Asymptomatic

## 3. Critical Stenosis = >60%, impending acute ischemic limb:

- rest pain
- ischemic ulceration
- gangrene



# PHYSICAL EXAMINATION:



Examination:	What do to:
Inspection Expose the skin and look for:	<ul style="list-style-type: none"><li>• Thick Shiny Skin</li><li>• Hair Loss</li><li>• Brittle Nails</li><li>• Colour Changes (pallor)</li><li>• Ulcers</li><li>• Muscle Wasting</li></ul>
Palpation	<ul style="list-style-type: none"><li>• Temperature (cool, bilateral/unilateral)</li><li>• Pulses: ?Regular, ?AAA</li><li>• Capillary Refill</li><li>• Sensation/Movement</li></ul>
Auscultation	<ul style="list-style-type: none"><li>• Femoral Bruits</li></ul>
Ankle Brachial Index (ABI)	= <u>Systolic BP in ankle</u> Systolic BP in brachial artery
Buerger's Test	<ul style="list-style-type: none"><li>• Elevate the leg to 45° - and look for pallor</li><li>• Place the leg in a dependent position 90° &amp; look for a red flushed foot before returning to normal</li><li>• Pallor at &lt;math&gt;&lt;20^\circ&lt;/math&gt; = severe PAD.</li></ul>

# THE 5 P'S

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- ✘ Peripheral signs of PVD are the classic 5 P's
  - Pulselessness
  - Paralysis
  - Paraesthesia
  - Pain
  - Pallor



# PICTURES:

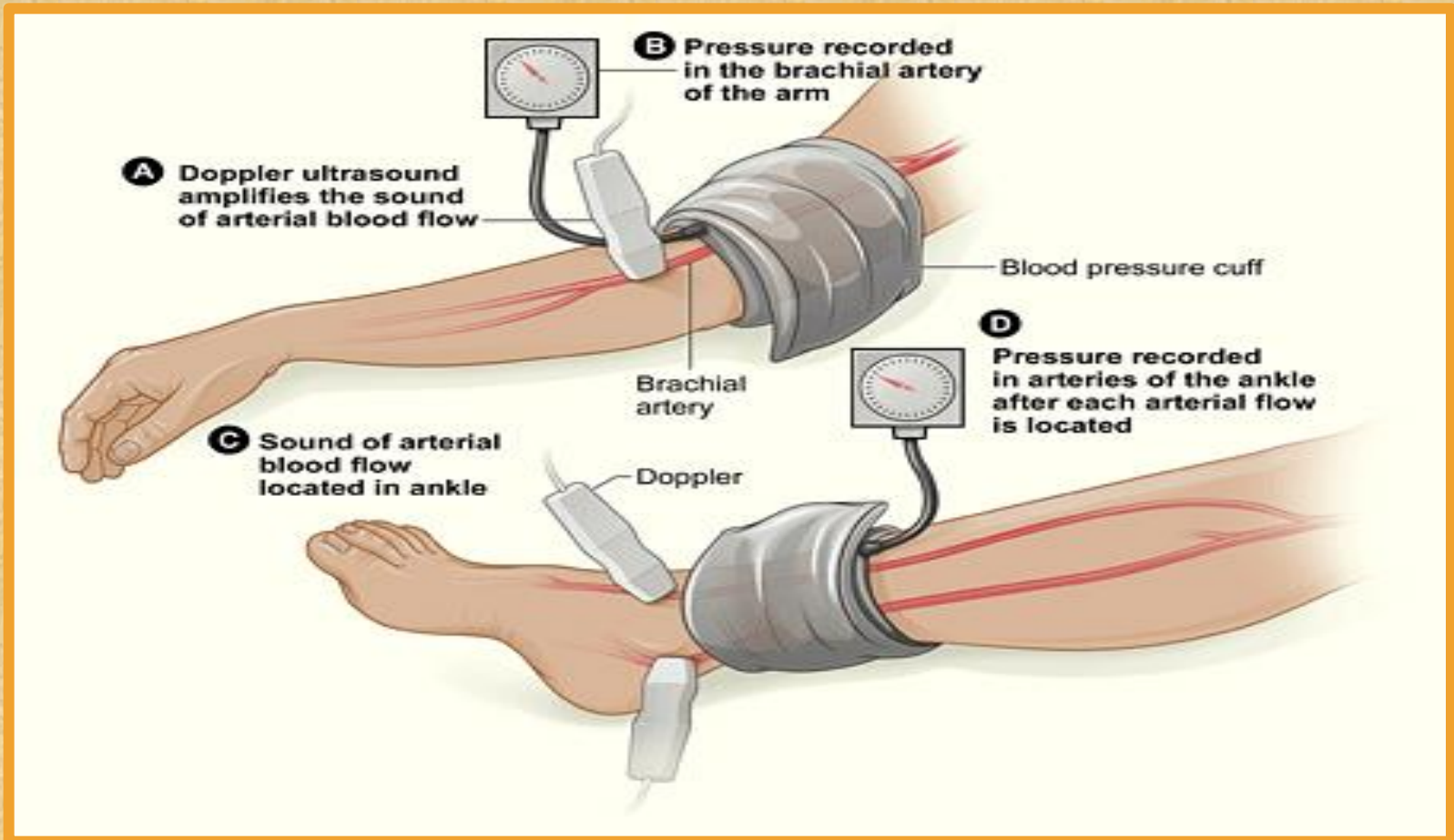


# PAIN SCALE

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- ✘ A subjective grading scale for PVD pain is as follows:
  - **Grade 1:** Definite discomfort or pain, but only of initial or modest levels (established, but minimal).
  - **Grade 2:** Moderate discomfort or pain from which the patient's attention can be diverted, for example by conversation.
  - **Grade 3:** Intense pain (short of Grade 4) from which the patient's attention cannot be diverted.
  - **Grade 4:** Excruciating and unbearable pain.

# WHAT DOES THE ABI MEAN?

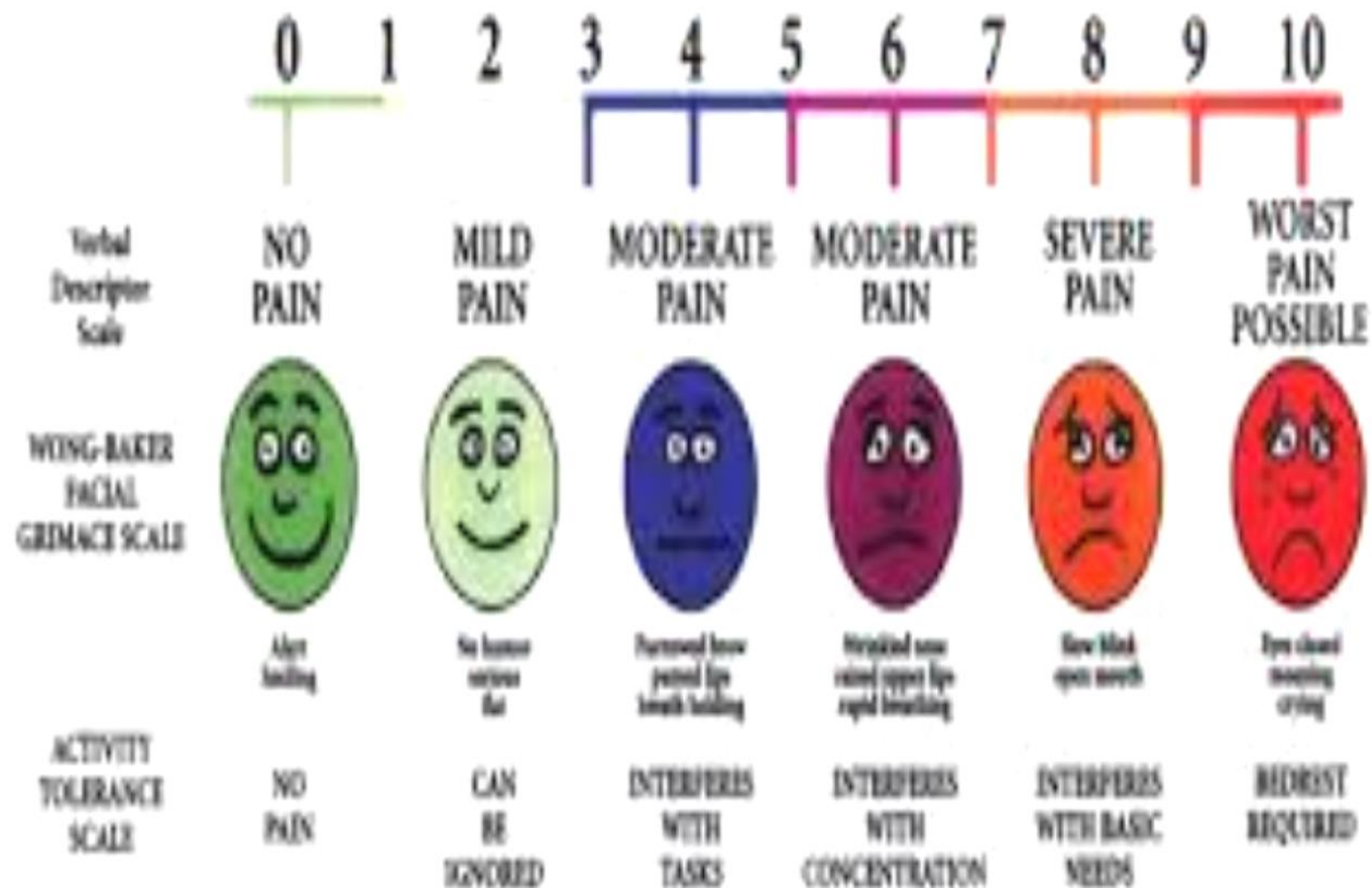


## CAUTION:

Patient's with Diabetes + Renal Failure:

They have calcified arterial walls which can falsely elevate their ABI.

This pain assessment tool is intended to help patient care providers assess pain according to individual patient needs. Explain and use 0-10 Scale for patient self-assessment. Use the faces or behavioral observations to interpret expressed pain when patient cannot communicate his/her pain intensity.



# INVESTIGATIONS:

## BLOOD TESTS:

1. FBE/EUC/Homocysteine Levels
2. Coagulation Studies
3. Fasting Lipids and Fasting Glucose
4. HBA1C

## WHEN TO IMAGE:

1. To image = to intervene
2. Pt's with disabling symptoms where revascularisation is considered
3. To accurately depict anatomy of stenosis and plan for PCI or Surgery
4. Sometimes in pt's with discrepancy in hx and clinical findings

## NON INVASIVE:

### Duplex Ultrasound

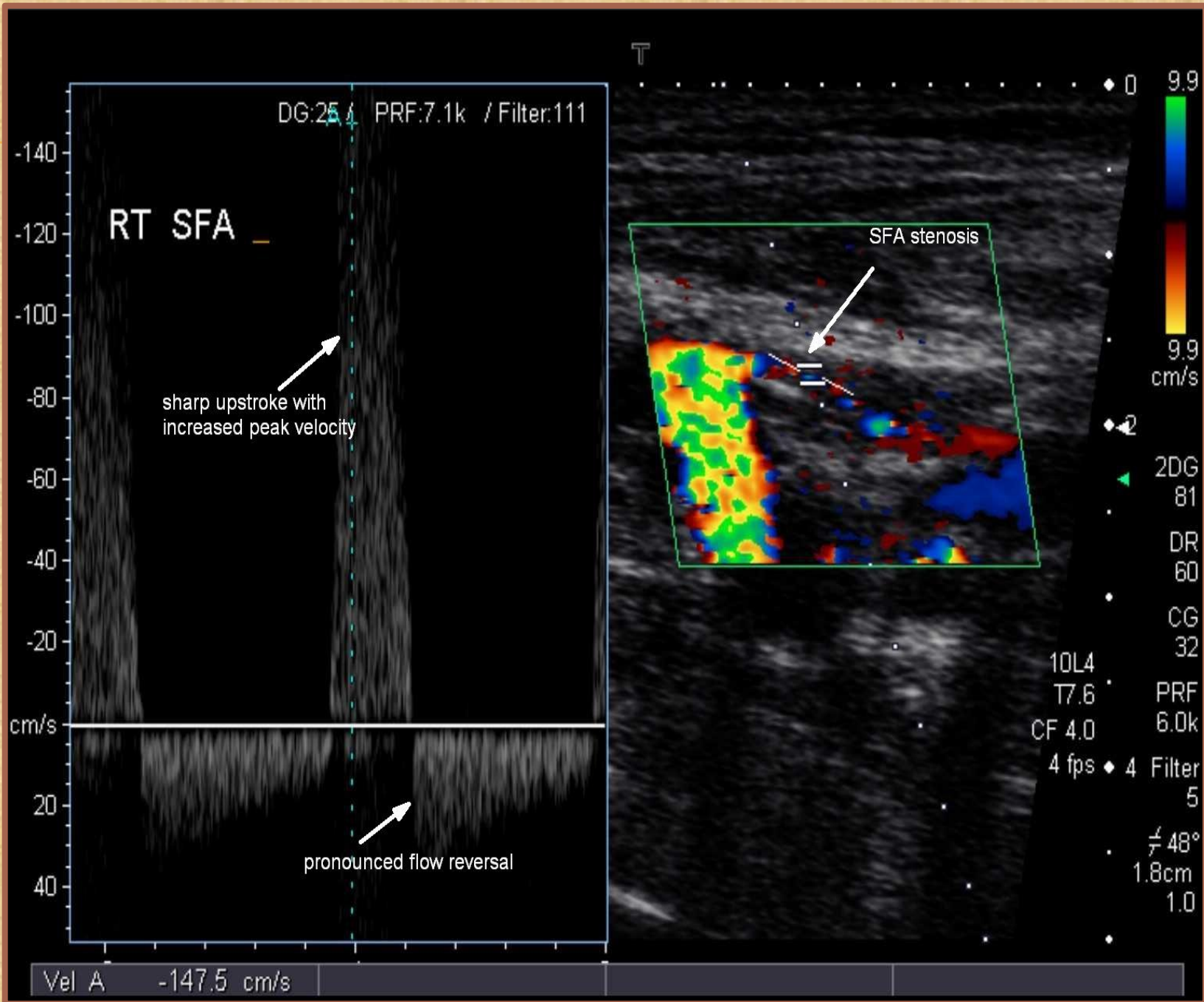
→ normal is triphasic → biphasic → monophasic → absent

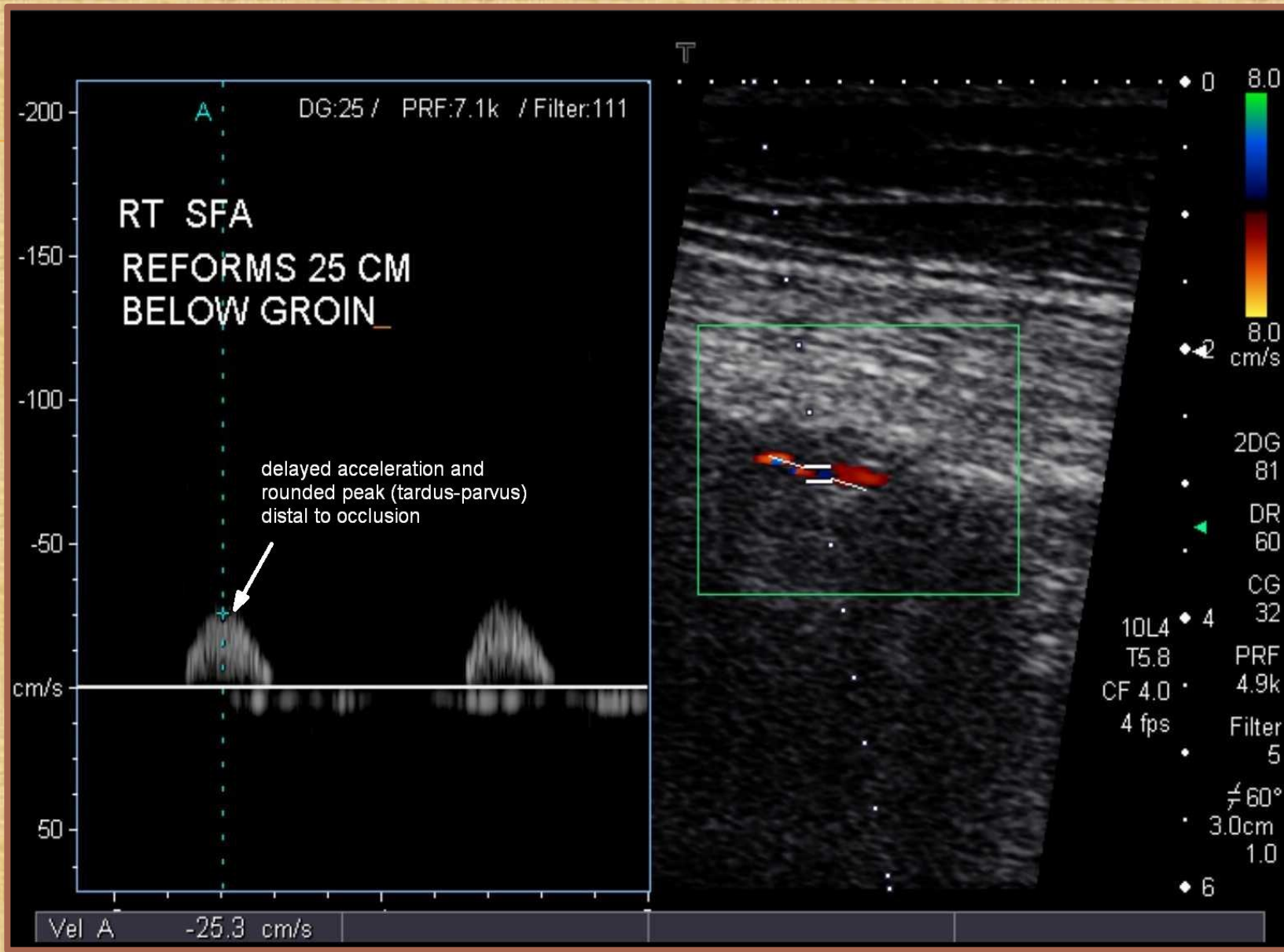


Normal

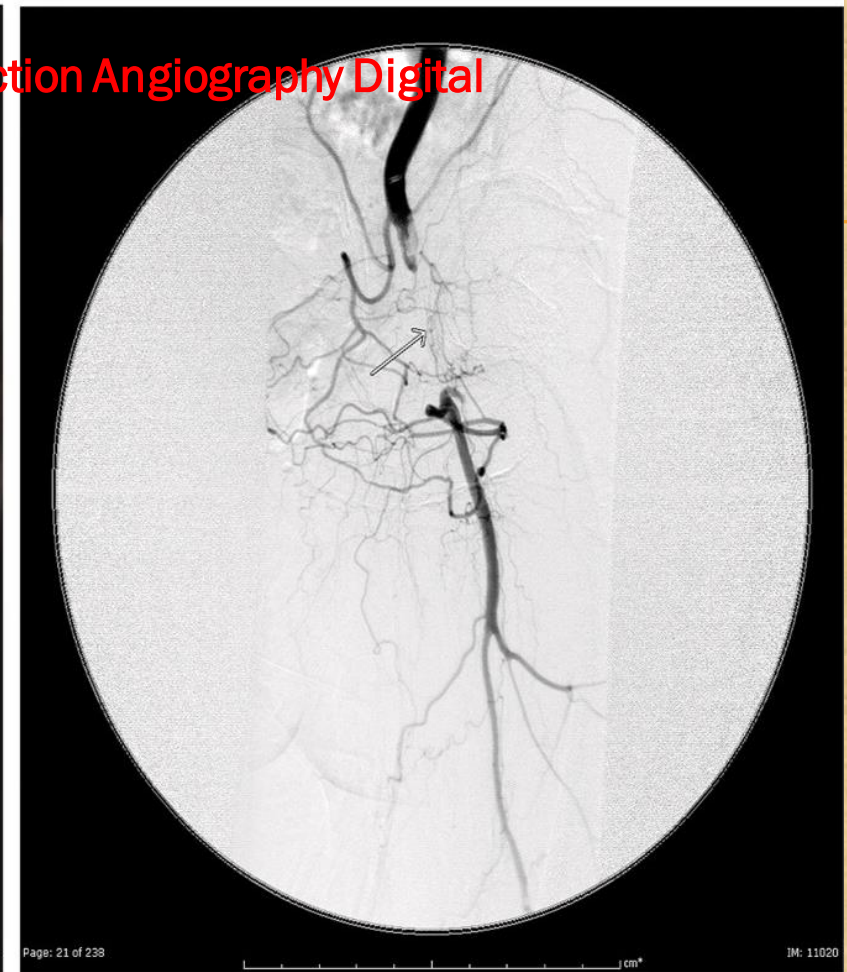
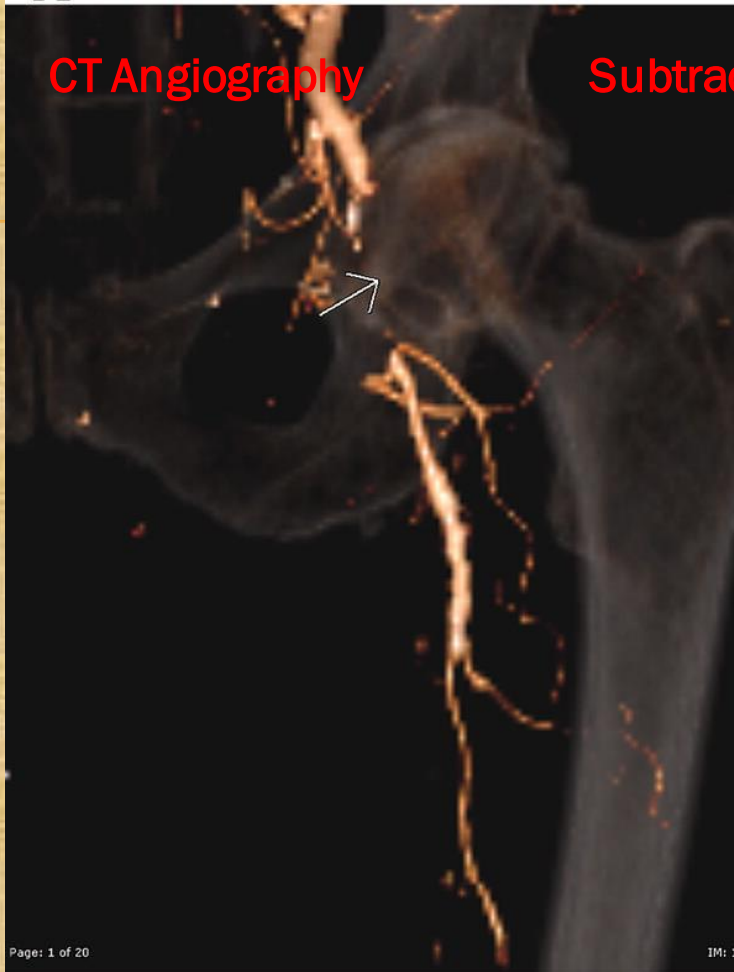


Progressive disease





TARDUS ET PARVUS = SMALL AMPLITUDE + SLOW RISING PULSE



## Value of angiography

- Localizes the obstruction
- Visualize the arterial tree & distal run-off
- Can diagnose an embolus:

*Sharp cutoff, reversed meniscus or clot silhouette*



# TREATMENT FOR PVD

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- ✘ Severe lower extremity PVD is treated initially with cardiovascular disease risk factor modification:
  - Exercise training
  - Medication
  - Diet
  - Stop Smoking
  - Interventional Radiology
  - Surgery
  - Gene-Based Therapy

# EXERCISE PRESCRIPTION

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## ✘ Duration

### ➤ Initial

✘ 35 minutes (intermittent walking)

### ➤ Subsequent

✘ Add 5 minutes every session until 50 minutes (intermittent walking) is possible

# EXERCISE PRESCRIPTION

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## ✘ Frequency

- 3-5 times per week.

## ✘ Specificity of Activity

- Treadmill walking is the recommended exercise.

# STOP SMOKING

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- ✘ On average, smokers are diagnosed with PVD as much as 10 years earlier than non-smokers.
- ✘ Stopping smoking now is the single most important thing you can do to halt the progression of PVD or prevent it in the future.

# MEDICATIONS

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- ✘ Drugs that lower cholesterol or control high blood pressure.
- ✘ Decrease blood viscosity.
  - Trental, Persantine, or Coumadin
- ✘ Antiplatelet agents

# GENE-BASED THERAPY

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- ✘ The field of molecular genetics has provided new understanding of vascular physiology and pathology and has opened exciting frontiers in the treatment of PVD.
- ✘ Direct gene transfer by intramuscular injection of DNA encoded with vascular growth factors has resulted in growth of new vessels and collateral circulation in chronically occluded lower extremity arterial vessels.

# SURGICAL TREATMENTS FOR PVD

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✘ Thrombectomy

✘ Bypass Grafts

**6-30-97 94 yr. old female Right side/Right foot  
Peripheral Vascular Disease 1.8 x 5 cm**



**4-29-97 94 yr. old female Right side/Right foot  
Peripheral Vascular Disease 4.3x7 x 0.2 cm**





# ADRENAL STEROIDS

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- ✘ The adrenal glands are located immediately superior to the kidneys.
- ✘ There are three classes of adrenal steroids:
  - mineralocorticoids,
  - glucocorticoids, and
  - androgens

# ORGANIZATION OF THE ADRENAL GLAND

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There is an adrenal cortex and adrenal medulla.

Steroids are made in three zones of the adrenal cortex:

**mineralocorticoids:** zona glomerulosa

**glucocorticoids:** zona fasciculata

**androgens:** zona reticularis

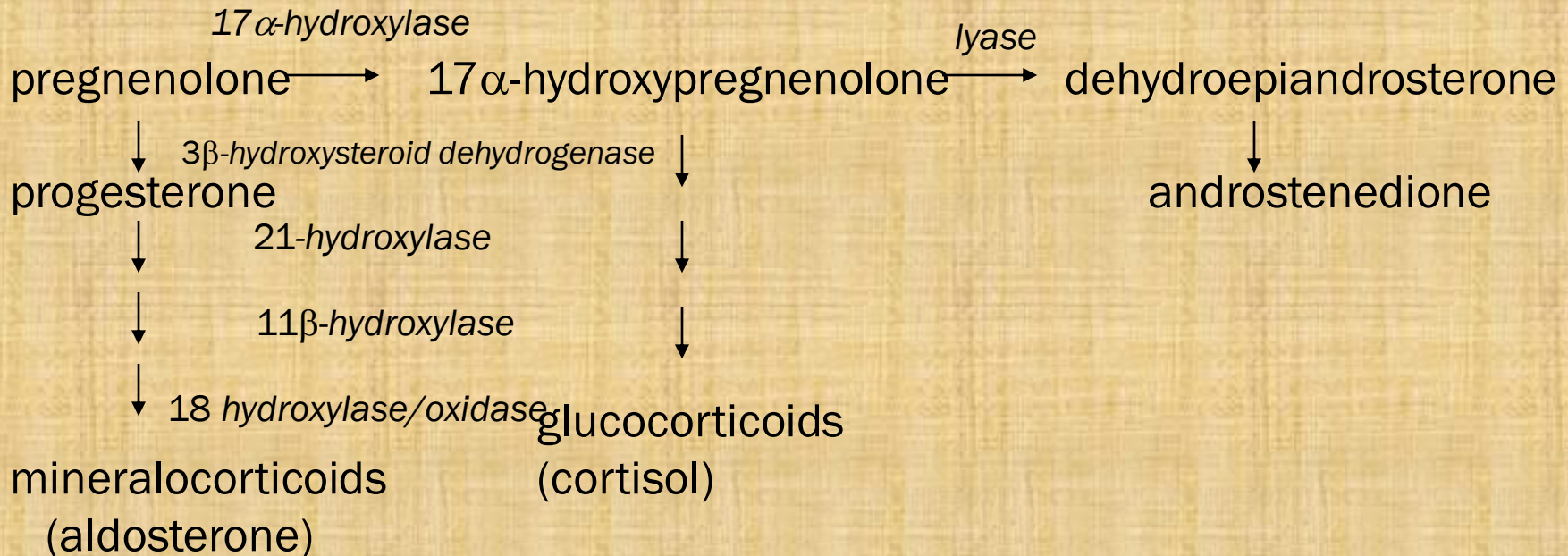
(What's made in the adrenal medulla??)

# ADRENAL STEROIDOGENESIS

- ✘ The first **enzymatic** step is the conversion of cholesterol to pregnenolone, which occurs in the mitochondria.
- ✘ This reaction is carried out by the enzyme, cytochrome P450 side-chain cleavage (P450<sub>scc</sub>; also called desmolase, or CYP11A1).
- ✘ This is a *rate limiting, nonreversible* step in the initiation of steroid biosynthesis.
- ✘ This step occurs in adrenal, ovary, and testis.

# ADRENAL STEROIDOGENESIS

- Next, pregnenolone can be converted into three different pathways, depending upon whether you want to make mineralcorticoids, glucocorticoids, or androgens:



# PRODUCTION OF STEROIDS IN THE TESTIS

- ✘ The **main** steroid produced in the male is testosterone, from the testis. In addition, the testis makes some androstenedione, dihydrotestosterone, and estradiol.
- ✘ In the male, there is peripheral conversion of testosterone to **dihydrotestosterone** (in androgen target tissues, like muscle) and **estradiol** (mostly in adipose tissue).

# ORGANIZATION OF THE TESTIS

- ✘ The testis is organized into two main parts:
  - **seminiferous tubules**: production of sperm cells, location of Sertoli cells (stay tuned...)
  - **interstitial tissue**: outside of the seminiferous tubules; the steroidogenic cell is the **Leydig** cell

# Pathway of Testosterone Production in the Testis

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- ✘ The production of androgens from cholesterol is identical to that in the adrenal, except that it continues from androstenedione to testosterone.

17 $\beta$ -hydroxysteroid  
oxidoreductase



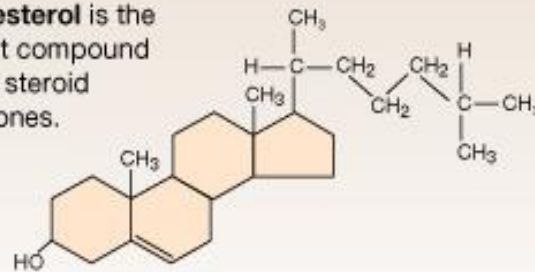
# TESTOSTERONE METABOLISM

- ✘ Testosterone can then be converted (mostly in peripheral tissues) to:
  - DHT (dihydrotestosterone) by  $5\alpha$ -reductase, or to
  - estradiol (E2) by cytochrome P450 aromatase



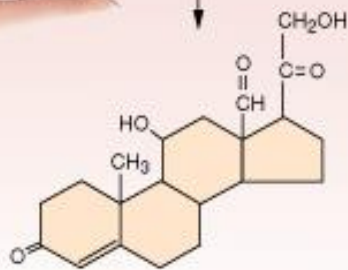
# STEROID HORMONES: REVIEW THE STRUCTURE

**Cholesterol** is the parent compound for all steroid hormones.

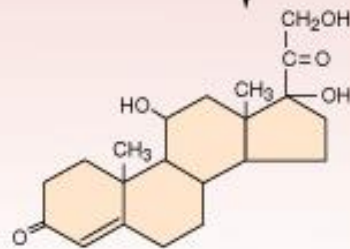


*modified by enzymes to make steroid hormones such as*

**In adrenal cortex**

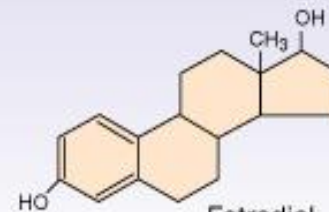


Aldosterone



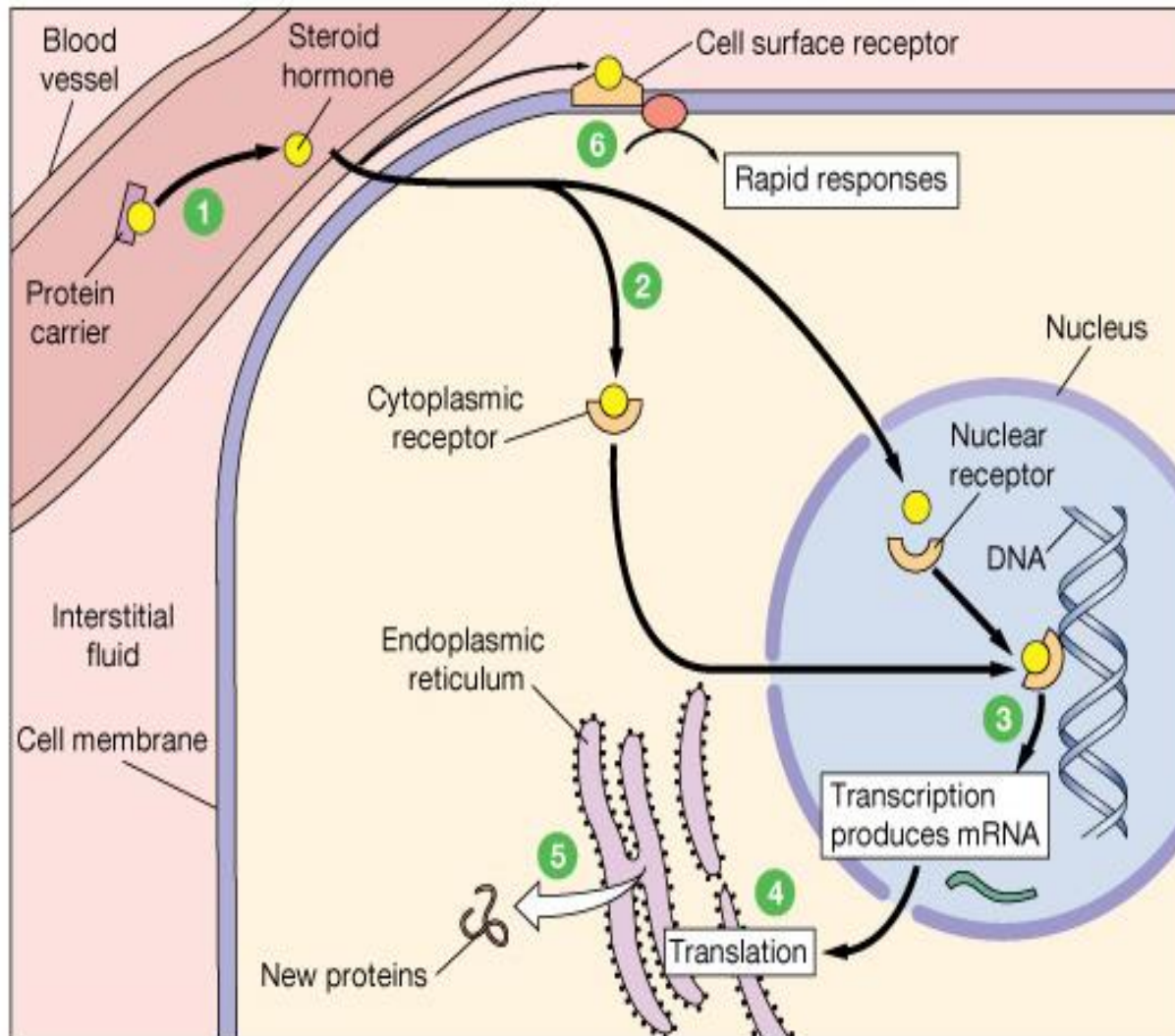
Cortisol

**In ovary**



Estradiol  
(an estrogen)

# STEROID HORMONES: MOLECULAR ACTION



**1** Most hydrophobic steroids are bound to plasma protein carriers. Only unbound hormones can diffuse into the target cell.

**2** Steroid hormone receptors are in the cytoplasm or nucleus.

**3** The receptor-hormone complex binds to DNA and activates or represses one or more genes.

**4** Activated genes create new mRNA that moves back to the cytoplasm.

**5** Translation produces new proteins for cell processes.

**6** Some steroid hormones also bind to membrane receptors that use second messenger systems to create rapid cellular responses.



# **RELATION BETWEEN LOW SERUM TESTOSTERONE LEVEL AND PERIPHERAL ARTERIAL DISEASE IN MEN AND CLINICAL EVALUATION OF EFFECT OF TESTOSTERONE ADMINISTRATION.**

**Guide: Dr Thrishuli P.B**

**Presenter : Dr Shivanand reddy K.V**

# NEED FOR STUDY

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- ✘ Peripheral artery disease (PAD) is one of the most common manifestation of atherosclerosis, affecting about 27 million individuals in India, Europe and North America.<sup>1</sup>
- ✘ As an early indicator of PAD, a low ankle-brachial index (ABI) has also been associated with increased risk of subsequent cardiovascular disease (CVD) and mortality.<sup>4</sup>

- 
- ✘ Several prospective investigations have shown that low total testosterone (TT) concentrations in men were associated with a less favorable cardiovascular risk profile including obesity, incident metabolic syndrome, diabetes mellitus, dyslipidemia, hypertension, mortality and PAD.<sup>5</sup>
  - ✘ Given the suggested associations of testosterone, ABI and PAD it is intriguing that data relating circulating testosterone concentrations to ABI and PAD are very limited.

- 
- ✘ Thus evidence for a prospective association of sex hormones with PAD is lacking to date.
  - ✘ Accordingly, we would investigate the associations of circulating testosterone concentrations with ABI and PAD.
  - ✘ Several lines of evidence support a role for testosterone in atherosclerotic disease in men.
  - ✘ Prevalence of cases of PAD with non-reconstructable critical limb ischemia is 13%.<sup>5</sup>

# REVIEW OF LITERATURE

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- ✘ Peripheral arterial disease is most common among the men, especially chronic smokers and its incidence in India is 1 in 5000 men.
- ✘ Testosterone causes vasodilation of the peripheral arteries by acting on the endothelium of the vessels and in turn results in release of nitric oxide(NO) which is a vasodilator and helps in vasodilatation of the vessels.<sup>1-2</sup>
- ✘ A study done by Asativestein et al. has shown that Serum testosterone associates positively with ABI.

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- Fowkes FG et al. has shown that short term administration of testosterone induces a beneficial effect in men with peripheral artery disease and the effect may be related to a direct peripheral artery-relaxing effects.<sup>2</sup>
  - A study done by Resnick HE et al. concluded that short term administration of testosterone induces a sex-independent vasodilation in peripheral conductance in men.<sup>3</sup>
  -



- 
- A study done taking subjects from Framingham heart study found that men with lower free testosterone had a significantly lower ankle-brachial index , similarly a higher free testosterone levels showed a protective effect on prevalent PAD in men.<sup>4</sup>
  - A cross-sectional study done by Hans Jutberger et al. revealed the observations of acute anti ischemic effect of testosterone in men with peripheral artery disease assessed using ankle brachial pressure index.<sup>5</sup>

- 
- ✘ As the literature shows that further research is required in this field to know the role of testosterone in peripheral arterial disease ,so we have taken up this study and to assess how a naturally produced hormone in the human body testosterone ,can relieve the male patients with critical limb ischemia of the symptoms.

# AIM OF THE STUDY

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- ✘ 1-To assess the association between low serum testosterone level and peripheral artery disease in men.
- ✘ 2-To evaluate the effect of acute administration of testosterone on peripheral artery disease in men.

# MATERIAL AND METHODS:

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- × 7.2 Source of data
- × Pts coming to JSS hospital surgery out- patient and emergency department.
- × **Study design:** Interventional study.

- **Sample size:** 20 pts calculated using the formula for sample size:

- $$S = z^2 f q / d^2$$
  
( $z = 1.96, f = 84 / 1582 = 0.053, q = 0.947, d = 0.05$ )

- Prevalence of peripheral arterial disease among males at our hospital in a year is 168 patients out of 1582 total admissions in the department of surgery. According to the formula my sample size comes to **40** patients.
- **Duration of study :** 1 year 4 months. (June 2013 to october 2014)

# INCLUSION CRITERIA:

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- 1. All male patients with critical limb ischemia with ABPI  $<0.3$ .
- 2. All male patients where other treatment modalities available have failed or not feasible.
- 3. All patients where bypass and endovascular procedures cannot be performed due to foresaid reasons:
  - a) Patient not fit for surgery having other co-morbidities.
  - b) Financial constraints of the patient to undergo vascular procedures.

# EXCLUSION CRITERIA:

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- ✘ 1. All male patients with  $ABPI > 0.4$
- ✘ 2. All male patients where other conventional modalities of treatment are feasible.
- ✘ 3. All male patients with PAD associated with malignancies like carcinoma prostate, Carcinoma lungs etc.



- 
- ✘ After examination of the patient either in OPD or Emergency department, ankle brachial pressure index will be assessed and depending on the value and other aspects of inclusion criteria patients will be taken into study and patients will be given intramuscular injection of testosterone thrice a week for three weeks, after taking prior consent, and effect of the drug will be assessed depending on the improvement in the walking distance, ankle-brachial pressure index(ABPI) and symptomatic relief of pain which will be assessed using pain scale of 0 to 10 (VAS).



# STATISTICAL METHODS:-

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- ✘ 1.Descriptive statistics
- ✘ 2.t-test-paired samples
- ✘ 3.chi-square test
- ✘ 4.Cross-tabulation ( contingency co-efficient test)
- ✘ 5.will be analysed using SPSS version 18

# INVESTIGATION:

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- ✘ Serum free testosterone levels.
- ✘ Serum PSA levels.

**TABLE 3 : Normal testosterone levels according to age**

<b>AGE</b>	<b>FREE TESTOSTERONE LEVELS(ng/ml)</b>
<b>0-5 yrs</b>	<b>75-400</b>
<b>6-9 yrs</b>	<b>70-200</b>
<b>10-11 yrs</b>	<b>70-230</b>
<b>12-13 yrs</b>	<b>70-400</b>
<b>14-15 yrs</b>	<b>70-450</b>
<b>16-19 yrs</b>	<b>100-600</b>
<b>19-25 yrs</b>	<b>500-1200</b>
<b>25-35 yrs</b>	<b>600-1200</b>
<b>35 + yrs</b>	<b>Decreases by 1 % per year</b>

# RESULTS

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- ✘ Total of 40 patients included in the study ,all are males.
- ✘ Age group (yrs)
- ✘ 28-45 : 32
- ✘ > 55 : 08.
- ✘ PSA levels mean :  $2.8 \pm 0.8$

# Table 1

<b>Factor</b>	<b>Prevalence or Mean <math>\pm</math> SD</b>
<b>AGE</b>	<b>40.2<math>\pm</math>8.4</b>
<b>SMOKING (%)</b>	
Never	<b>4.2</b>
Previous	<b>14.4</b>
Current	<b>81.6</b>
<b>BMI (KG/m<sup>2</sup>)</b>	<b>26.4<math>\pm</math>3.5</b>
<b>HTN(%)</b>	<b>35.4</b>
<b>DIABETES (%)</b>	<b>9.3</b>
<b>ABI ( &lt; 0.4)%</b>	<b>92.5</b>
<b>FREE TESTOSTERONE (ng/dl)</b>	<b>270<math>\pm</math>82</b>
<b>SHBG (nmol/l)</b>	<b>43.2<math>\pm</math>21.9</b>
<b>PSA (ng/ml)</b>	<b>2.8<math>\pm</math>0.9</b>

**Table 2 : Univariate associations between serum testosterone level and ABI**

<b>TESTOSTERONE</b>	<b>0.051</b>	<b>&lt; 0.001</b>
<b>FREE TESTOSTERONE</b>	<b>0.050</b>	<b>&lt; 0.001</b>
<b>SHBG</b>	<b>0.013</b>	<b>0.51</b>

# RESULTS CONT...

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- ✘ 38 patients had testosterone level lower than normal for their age, which was statistically significant with P value of  $< 0.001$ .
- ✘ 36 patients had ABI less than 0.4 and had rest pain.
- ✘ PSA levels were normal for all the patients and prostate cancer was excluded.

- 
- ✘ Among 40 patients 36 patients had improvement in ABI on an average of  $0.4 \pm 0.2$ , which was statistically significant with p value of  $<0.001$
  - ✘ 32 patients walking distance was improved on an average about  $500 \pm 100$  mts ,with p value of  $<0.005$ .
  - ✘ On VAS scale patients had improvement in their pain from 8 to 3 on an average.



# DISCUSSION

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- ✘ Accumulating data support a strong association of low level testosterone in peripheral artery disease in men.
- ✘ However, the relationship between serum testosterone and lower extremity PAD requires further study.

- 
- ✘ We show here that circulating free testosterone positively associates with critical ABI values in men, indicating a negative association between testosterone and the degree of peripheral arterial disease in the lower extremities.
  - ✘ Furthermore, when lower extremity PAD was defined as an ABI 0.90, we found that low serum testosterone (in the lowest quartile) associate with lower extremity PAD.

- ✘ The present study reports a negative association between serum testosterone levels and lower extremity PAD in men. This result is in agreement with previous studies reporting a negative association between serum testosterone levels and carotid intima-media thickness (3 to 5) as well as cross-sectional studies showing a consistent inverse relationship between endogenous testosterone and male cardiovascular events (6).
- ✘ However, no studies have established a significant relationship between circulating testosterone and incident peripheral arterial disease in men (6,8). In most animal studies, testosterone treatment inhibits peripheral arterial disease in male species; and testosterone is a vasodilator in men with established arterial disease (6).

✘ However, no current interventional study has sufficient power to assess a possible protective effect of testosterone on human peripheral arterial disease(6,24).

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✘ In comparison, our previous data from the MrOS Sweden cohort demonstrate that testosterone positively with bone mineral density in men (16).

- 
- ✘ Our study show a significant improvement in patients clinical status post testosterone administration ,in which out of 40 patients included in the study 32 were of the age group 28-45 and 8 patients were above the age of 55.
  - ✘ All the 40 patients had significant decrease in the testosterone levels for their age and there has been significant improvement in walking distance ,ABI improvement by 0.4,pain scale pain improvement on VAS from 8 to 3 after 9 doses of testosterone administration.

# OBSERVATIONS.

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- ✘ Low testosterone level is an independent risk factor for PAD in men which has not been researched in depth till now.
- ✘ Patients show tremendous improvement in symptoms post testosterone administration.
- ✘ We clinically postulate the theory that testosterone causes improvement in blood flow by release of NO and improves the symptoms in peripheral vessels.

- ✘ It would be a revelation in the field of vascular surgery where a natural sex hormone testosterone could help patients from recovering from a cripple disease without any invasive ,expensive,morbid interventions and improve patients standard of life.
- ✘ Further research is required at a greater level to further know the exact mode of its action in improvement in PAD in men.



THANK YOU