Biological systems, overview

Neil Pendleton
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Biomarkers in panel surveys: outline of session

- Provide background to the frequently available biomarkers in panel surveys (see ICLS handbook common survey measurements 2nd edition 2016)
- The aim to give overview key organs/systems, deeper understanding of practicalities of measurement and how to use them
- Divided into 2 parts: first with Neil Pendleton on selected organ systems and second part on the physical/physiological measures;
- Please ask questions at any time on anything

Endocrine system

- Definition is production of regulatory protein that travels distance from source tissue to place of action via blood
- They often act through a feedback regulation loop
- Often included as biomarkers in panel survey studies as collection feasible

Master regulator: Hypothalamus/Pituitary gland

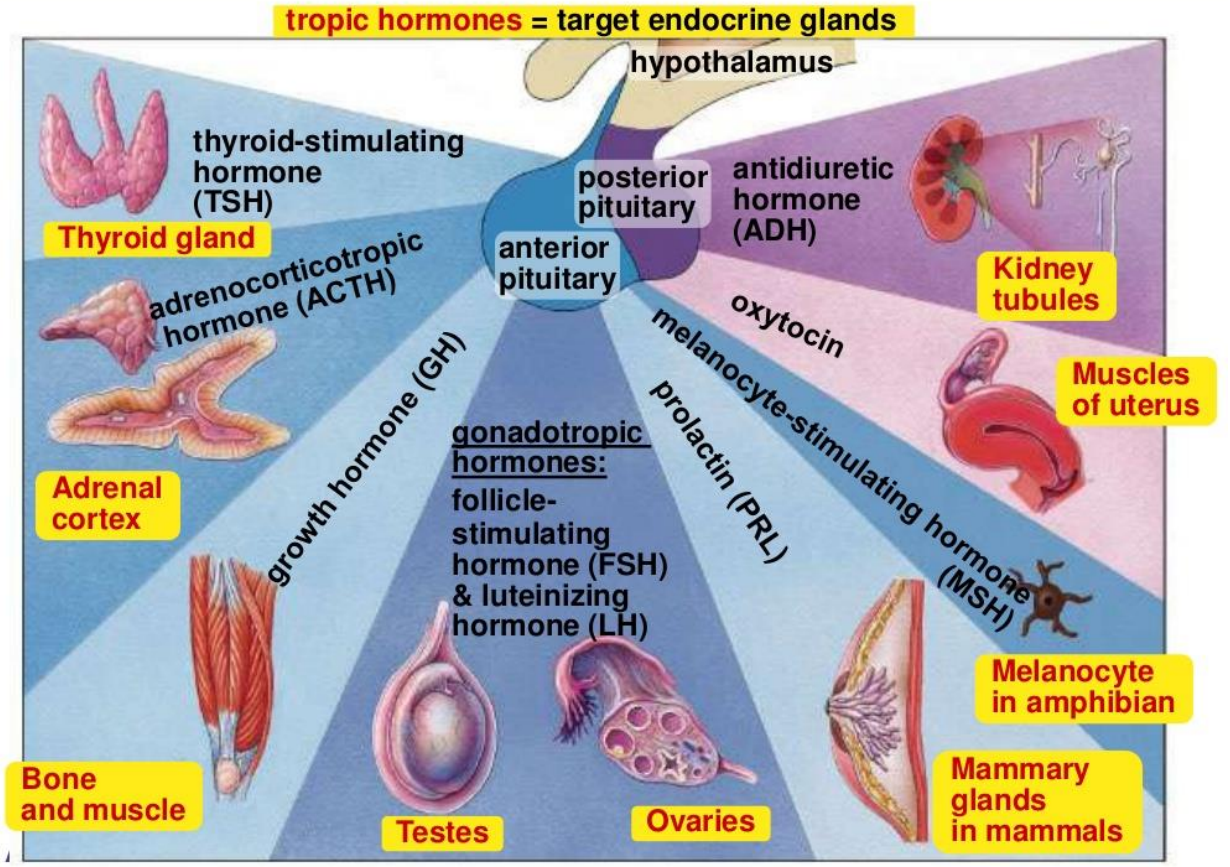
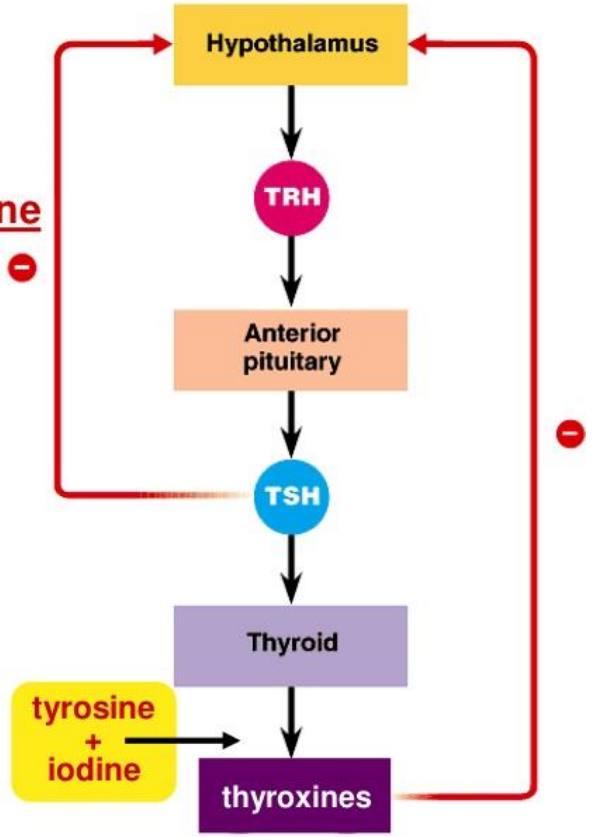


Image by Jay Swan 2011

Regulating metabolism

- **Hypothalamus**
  - TRH = TSH-releasing hormone
- **Anterior Pituitary**
  - TSH = thyroid stimulating hormone
- **Thyroid**
  - produces thyroxine hormones
  - metabolism & development
    - bone growth
    - mental development
    - metabolic use of energy
    - blood pressure & heart rate
    - muscle tone
    - digestion
    - reproduction



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Endocrine System Control

Regulation of Blood Sugar

Feedback

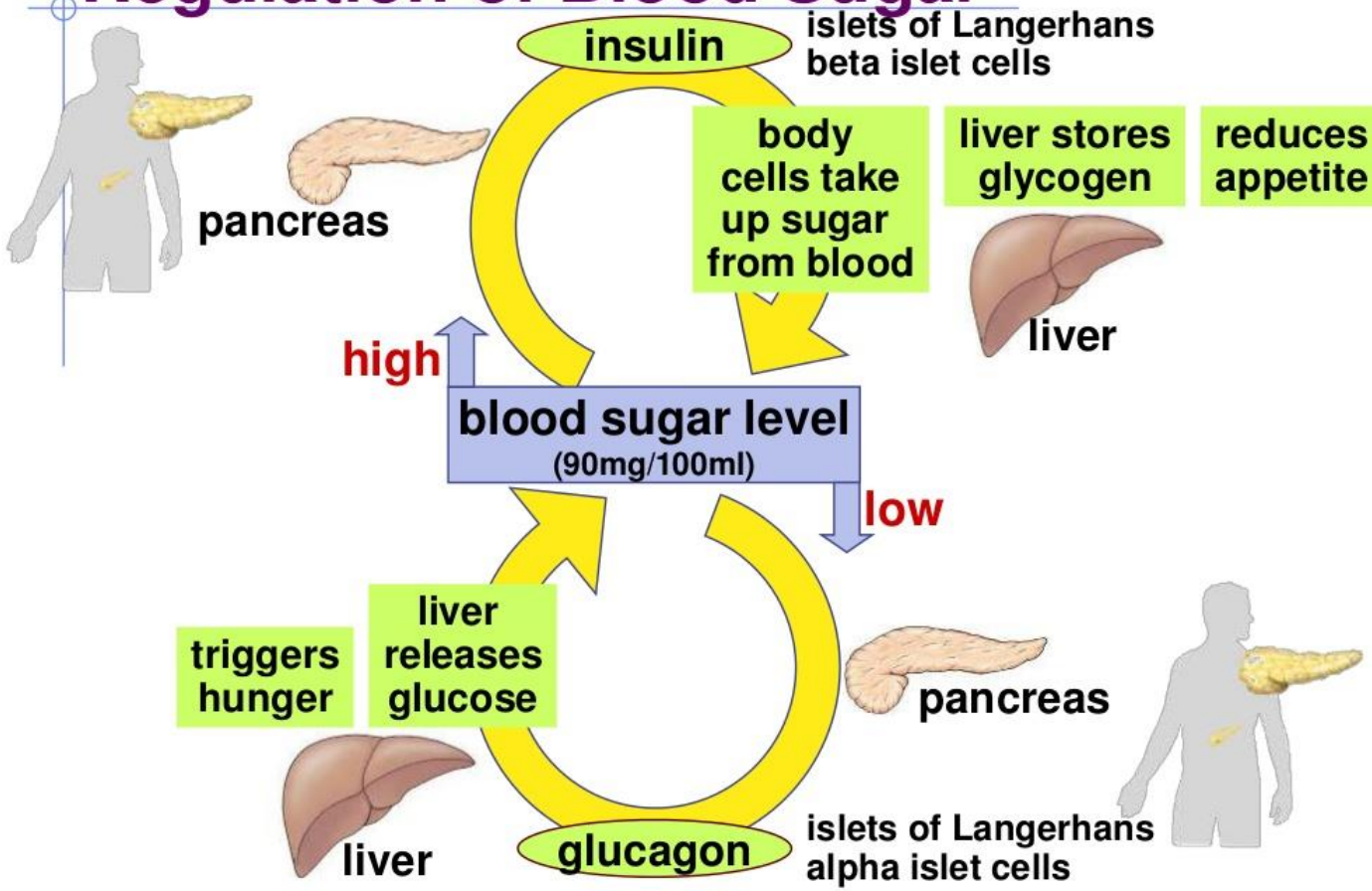
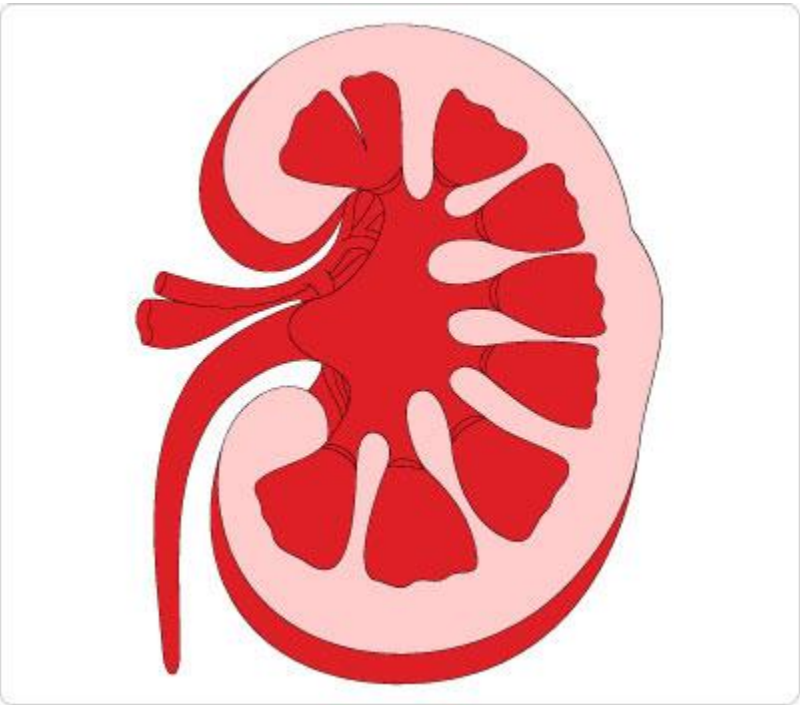


Image by Jay Swan 2011

Kidney function



- Regulation of body fluid volume and osmolality
- Regulation of electrolyte balance
- Regulation of acid base balance
- Excretion of waste products (urea creatinine ammonia drugs toxins)
- Retention of substances vital to body glucose and amino acids
- Regulation blood pressure
- Production and secretion of hormones renin erythropoietin
- Activation vitamin D

Functional renal anatomy
Nephron

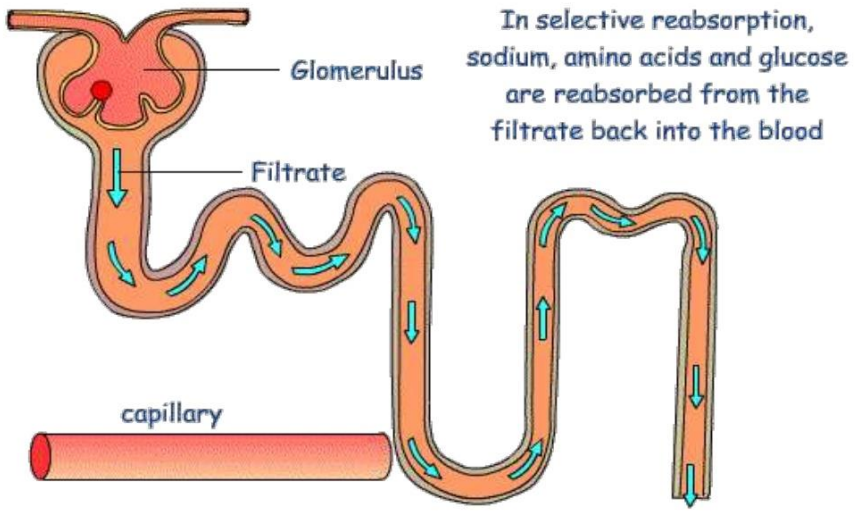


Image Tapeshwar Yadav 2016

Renal function tests

- Clearance tests: volume creatinine
- Calculation creatinine clearance
- Blood biochemistry
- Microalbuminuria and proteinuria

Estimated creatinine clearance

- Number of formula
- Cockcroft & Gault
- MDRD
- Note children use Scwartz or Counahan Barratt
- All use function of height plus serum creatinine

- **C&K equation**

Creatinine clearance **=** (((140 - age in years) x (wt in kg)) x 1.23) / (serum creatinine in micromol/l)

- **MDRD**

MDRD equation : 186 x (Creatinine/88.4)-1.154 x (Age)-0.203 x (0.742 if female) x (1.210 if black).

Biochemistry blood and urine

- Available in all routine test profiles
- Electrolyte levels sodium and potassium (calcium) phosphate)
- Metabolites creatinine and urea
- Protein levels
- Urine electrolytes sodium and potassium
- Microalbuminuria and proteinuria = renal damage diabetes and hypertension

Urinary chemistry

- Urine electrolytes sodium and potassium
- Microalbuminuria and proteinuria = renal damage diabetes and hypertension
- Clinical test is often the urine albumen/creatinine (ACR) ratio on single sample used to stage chronic kidney disease

Classification of Chronic Kidney Disease

NICE National Institute for Health and Care Excellence

Classification of chronic kidney disease using GFR and ACR categories

GFR and ACR categories and risk of adverse outcomes			ACR categories (mg/mmol), description and range		
			<3 Normal to mildly increased	3–30 Moderately increased	>30 Severely increased
			A1	A2	A3
GFR categories (ml/min/1.73m²), description and range	≥90 Normal and high	G1	No CKD in the absence of markers of kidney damage		
	60–89 Mild reduction related to normal range for a young adult	G2			
	45–59 Mild–moderate reduction	G3a[1]			
	30–44 Moderate–severe reduction	G3b			
	15–29 Severe reduction	G4			
	<15 Kidney failure	G5			

Increasing risk

Increasing risk

[1] Consider using eGFRcystatinC for people with CKD G3aA1 (see recommendations 1.1.14 and 1.1.15)

Abbreviations: ACR, albumin:creatinine ratio; CKD, chronic kidney disease; GFR, glomerular filtration rate

Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International (Suppl. 3): 1–150

Chronic Kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care NICE clinical guideline 182 (July 2014).

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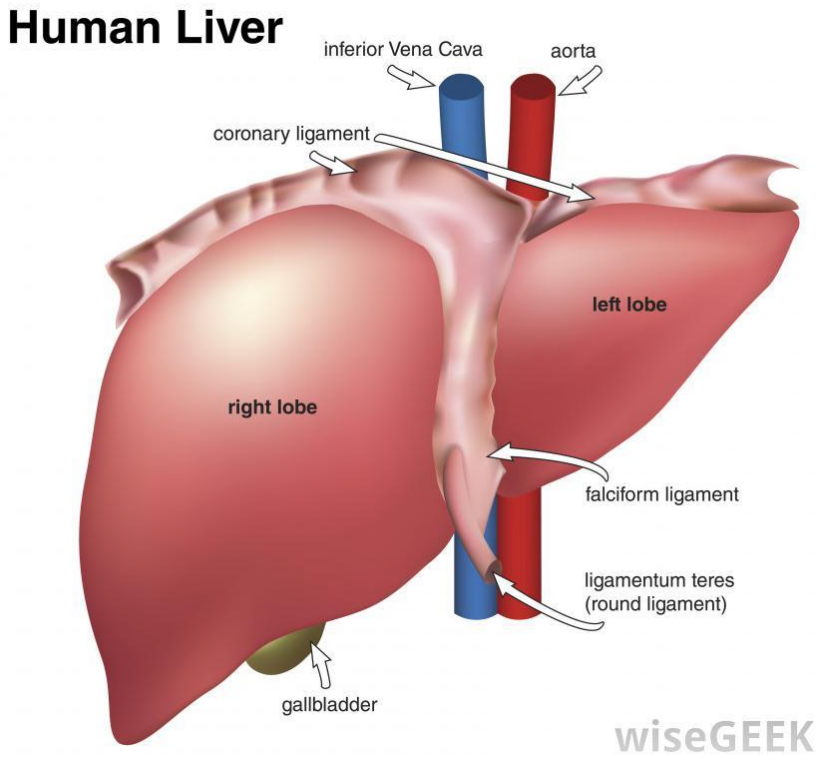
Liver anatomy

- Represents 2% of total body weight
- Weighs about 1300-1500om
- Located right upper quandrant of abdomen behind right ribs
- Surface 2/5
- Lobes 2/2



The Liver and Hepatic Function

- Formation and secretion of bile
- Nutrient and Vitamin metabolism
- Glucose and other sugars
- Amino acids
- Lipids
- Fatty Acids
- Cholesterol
- Lipoproteins
- Fat soluble vitamins
- Water soluble vitamins
- Inactivation of various substances
- Toxins
- Steroids
- Other hormones
- Synthesis of plasma proteins
- Acute phase proteins
- Albumin
- Clotting factors
- Steroid and other hormone binding proteins
- Immunity
- Kupffer Cels

Liver function tests
Implications

Biochemical Test	Clinical Implication of abnormality
Alanine amino transferase	Hepatocellular damage
Aspartate Amino Transferase	Hepatocellular damage
Bilirubin	Cholestasis, impaired conjugation or bile tract obstruction
Alkaline Phosphatase	Cholestasis, infiltrative disease (malignancy) or bile tract obstruction
Prothrombin time	Synthetic Function
Albumen	Synthetic Function
Gamma-glutamyl Transferase	Cholestasis or bile tract obstruction
5 nucleotidase	Cholestasis or bile tract obstruction

Liver function tests clinical interpretation

- Alanine aminotransferase and aspartate amino transferase are all associated with hepatitis, alcohol related and non alcoholic fatty liver disease (NAFLD). Alanine aminotransferase more specific for the liver (aspartate amino transferase linked to muscle cell damage also)
- Alkaline phosphatase linked to obstruction bile flow
- Gamma-glutamyl transferase associated with obstruction bile flow, NALFD but also with alcohol intake
- Bilirubin causes jaundice and linked to obstruction bile flow (also damage to red blood cells in some cases)
- Albumen lower levels associated with liver damage of any cause
- NOTE almost all instances the blood tests would be correlated with more information and imaging tests like ultrasound

Anthropometry

Anthropometry

- A branch of anthropology that involves the quantitative measurement of the human body
- Portable, inexpensive (equipment) and non-invasive assessment of size, proportion and composition of the human body
- Historical perspective including da Vinci and Galton

Adult anthropometric parameters

Basic measures

- Height (length)
- Weight (mass)
- Waist and hip circumference
- Mid upper arm circumference
- Skin fold thickness
- Triceps, Biceps, Subscapular and Supra-iliac

Derived measures

- BMI
- Waist hip ratio

Body Mass Index ranges and co-morbidity risk

QUANTIFYING OBESITY WITH BODY MASS INDEX (WEIGHT/HEIGHT²)

BMI (kg/m²)	CLASSIFICATION*	RISK OF OBESITY COMORBIDITY
18.5 - 24.9	Normal range	Negligible
25.0 - 29.9	Overweight	Mildly increased
>30	Obese	
30.0 - 34.9	Class I	Moderate
35.0 - 39.9	Class II	Severe
> 40.0	Class III	Very severe

$$\text{Body Mass Index} = \frac{\text{Weight (in kg)}}{\text{Height}^2 \text{ (in m)}}$$

WHO and International Obesity Task Force

Waist-to-Hip Circumference Ratio (WHR)

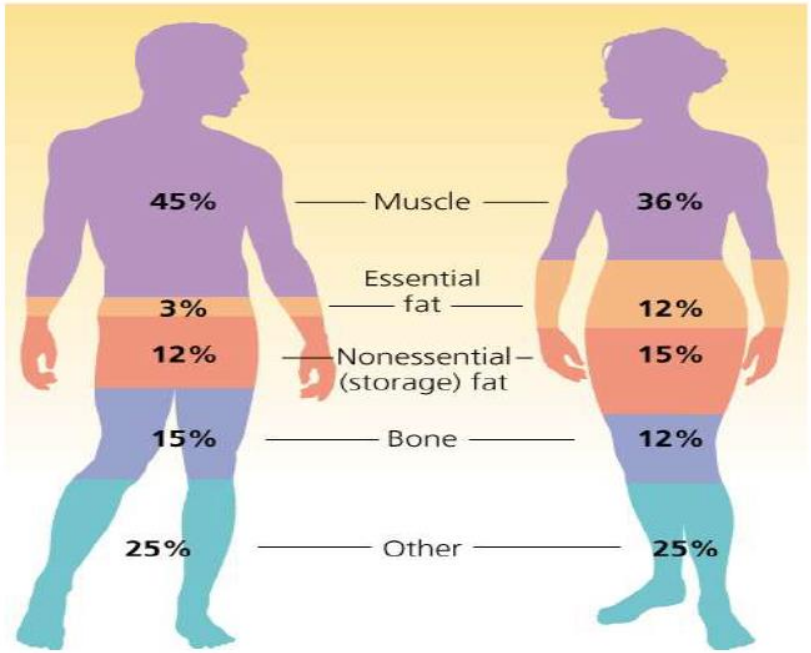
- Indicator of distribution of subcutaneous adipose tissue
- CHD risk linked to abdominal fat
- Gender and racial variation
- Women WHR 0.85-1.7 (high risk) <0.85 (low risk)
- Men 0.95-1.9 (high risk) <0.95 (low risk)
- Asians increased metabolic risk lower WHR

Image from Babakayode A Olagbaye 2017

Child anthropology

- These used to examine values with addition of age related growth patterns (Growth Velocity Charts)
- Some measures are more challenging in babies/infants with different equipment
- Unlike adults some are age dependent

Body composition



Dual X-Ray absorptiometry (DXA)

Bioelectric impedance Analysis(BIA)

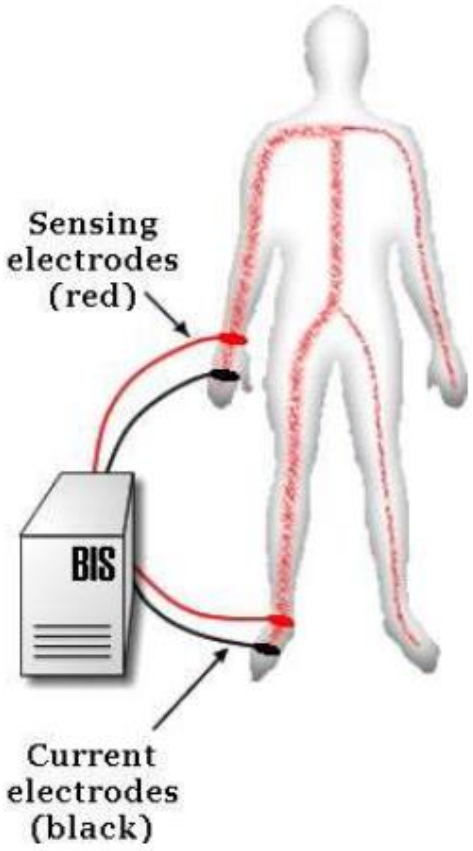
Infra-red spectroscopy

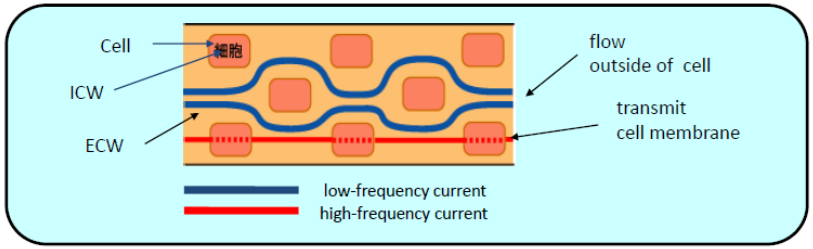
Ultrasound

Imaging techniques (DEXA)

Image by Fahmida Hashem 2015

Bio impendence

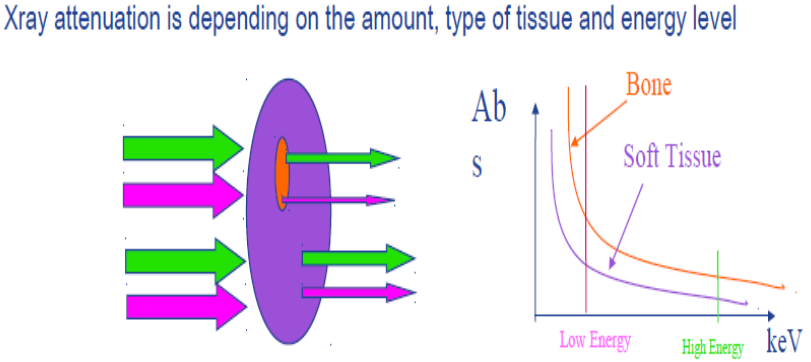




- Low frequency current is unable to pass the cell membrane and it flows outside the cell.
- High frequency current is able to penetrate the cell membrane and can also flow within the cell.

Image by Fahmida Hashem 2015

X-ray absorption and DEXA



- Principle of x-ray attenuation
- Bone higher attenuation than soft tissue

Image by Majid Abi SaaB 2015

DEXA

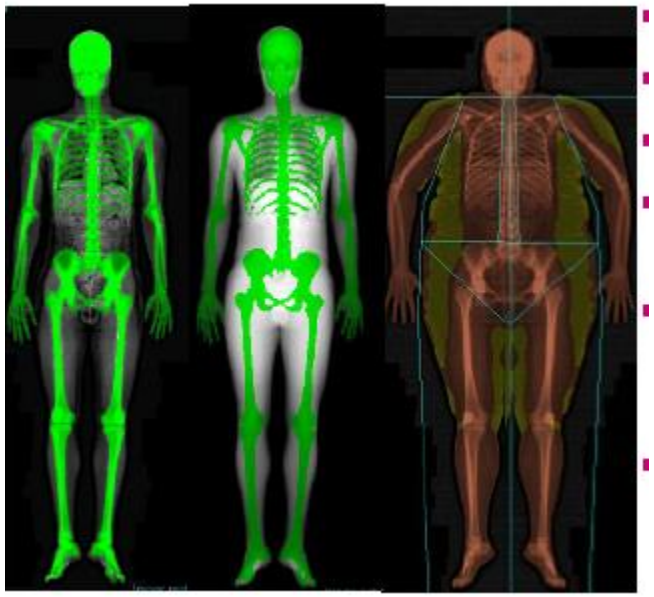


Image by Majid Abi SaaB 2015

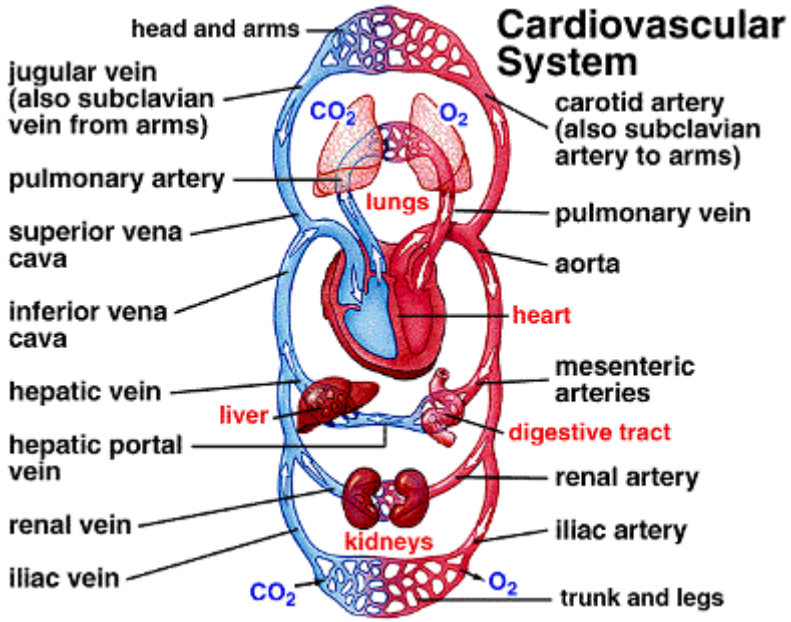
- Use 3 compartment model
- Define bone area
- Use 2 energies to calculate bone mass
- Calculate fat using area outside bone with 2 energies
- Use local uniform composition over bone region to calculate whole soft tissue region
- This permits estimation lean mass
- Examine bone, lean and fat masses for sub regions

Cardiovascular and Respiratory measures

Cardiovascular measures

Cardiovascular measures

- Common addition to human panel surveys
- Arterial blood pressure
- Electrocardiogram
- Heart rate variability
- Arterial (carotid) intimal thickness



Arterial blood pressure

- Understand the concept of mean blood pressure, systolic, diastolic, and pulse pressure and mean blood pressure.
- Understand normal variations in arterial blood pressure.
- Understand the relationship between cardiac output blood pressure and total peripheral resistance.
- Understand factors determining blood pressure.
- Regulation of arterial blood pressure

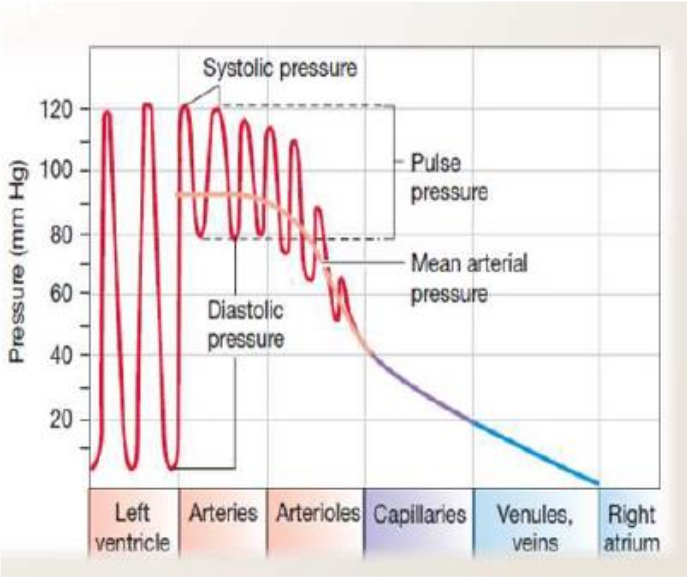


Image by Harsistha Sinivasan 2018

NHS
National Institute for
Health and Clinical Excellence

Hypertension in adults: diagnosis and management

3nd Edition August 2019

Clinical Guideline Implementation Tools

NICE clinical guideline 136

Background

- High Blood Pressure:
- Major risk factor for stroke, myocardial infarction, heart failure, chronic kidney disease, cognitive decline and premature death.
- Untreated hypertension can cause vascular and renal damage leading to a treatment-resistant state.
- Each 2 mmHg rise in systolic blood pressure associated with increased risk of mortality:
  - 7% from heart disease
  - 10% from stroke.

Epidemiology

- Hypertension is common in the UK population.
- Prevalence influenced by age and lifestyle factors.
- 25% of the adult population in the UK have hypertension.
- 50% of those over 60 years have hypertension.
- With an ageing population, the prevalence of hypertension and requirement for treatment will
  continue to increase.

Electrocardiogram

Electrocardiogram

- Measure of the electrical activity coordinating cardiac cycle across the 4 chambers
- 1924 - the noble prize for physiology or medicine is given to William Einthoven for his work on ECG
- Cardiac systole ventricular contraction=depolarization
- Cardiac diastole ventricular relaxation=repolarization (?atrial systole)

Electrocardiogram

- P wave= contraction of atria depolarisation
- QRS complex=ventricular depolarisation
- T wave=ventricular repolarisation
- ECG trace is collection of complexes over time so rhythm and rate can be observed

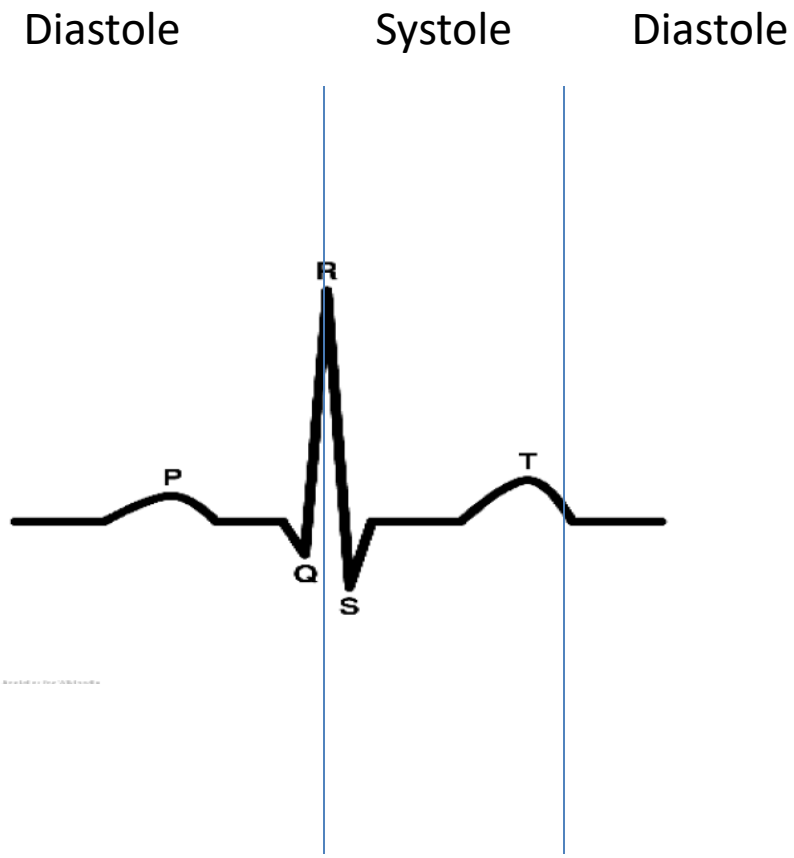


Image by Ragwhender Singh 2008

Electrocardiogram

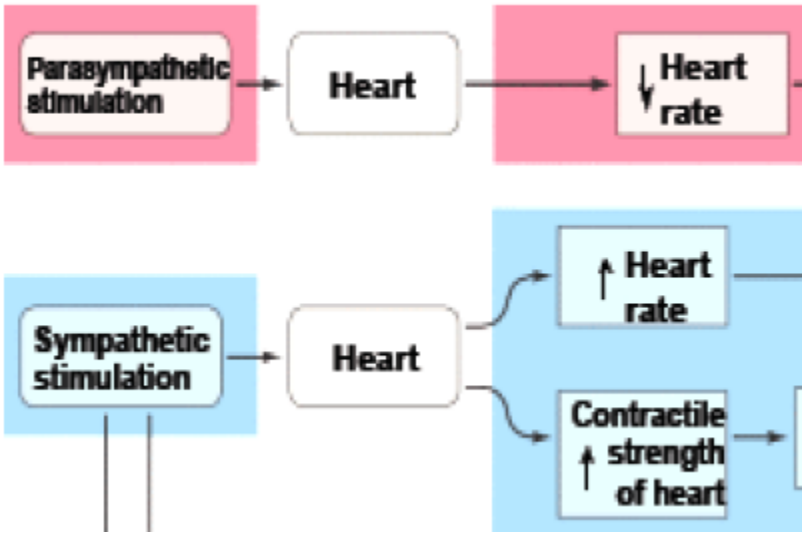
- Determined by primary pathologies of the heart such as cardiovascular disease
- Also affected by external factors such as exercise, emotional stress, pain, temperature, respiratory, hormonal factors, medicines and substance use
- Consider operator affects also such as lead positioning, body position

Image by Ragwhender Singh 2008

Heart Rate Variability

Heart Rate Variability (HRV)

- HRV is index of autonomic function
- Decrease in HRV increases risk arrhythmia and sudden cardiac death
- Associated with: depression; diabetes mellitus; heart failure; hypertension

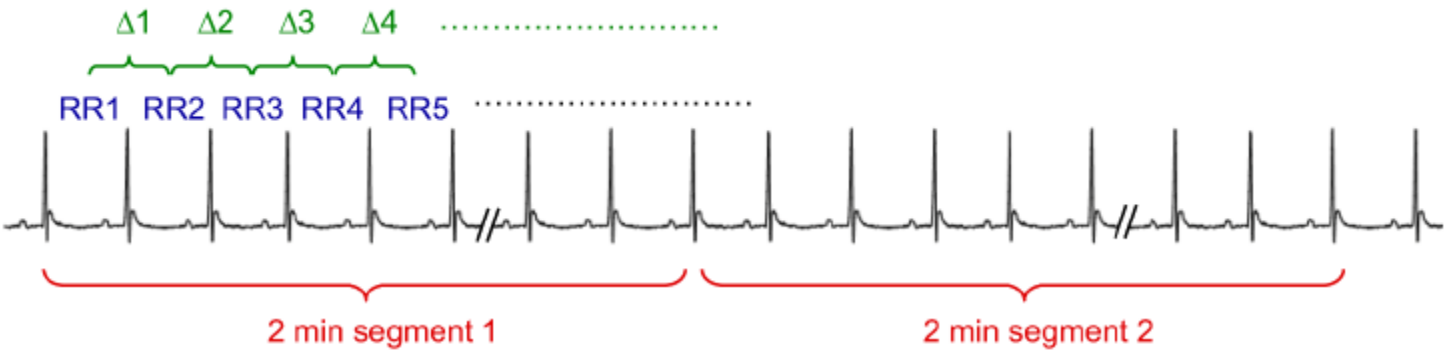


Courtesy Dr M Ababnah

Heart Rate Variability (HRV)

- HRV criterion is normal R-R interval
- Factors influencing data accuracy
- Quality of ECG wave forms
- Quality of data subjects vary
- Quantity data (day ~0.85M beats)
- Influenced by age, gender, disease status and medicines cf. ECG

Heart Rate Variability (HRV)

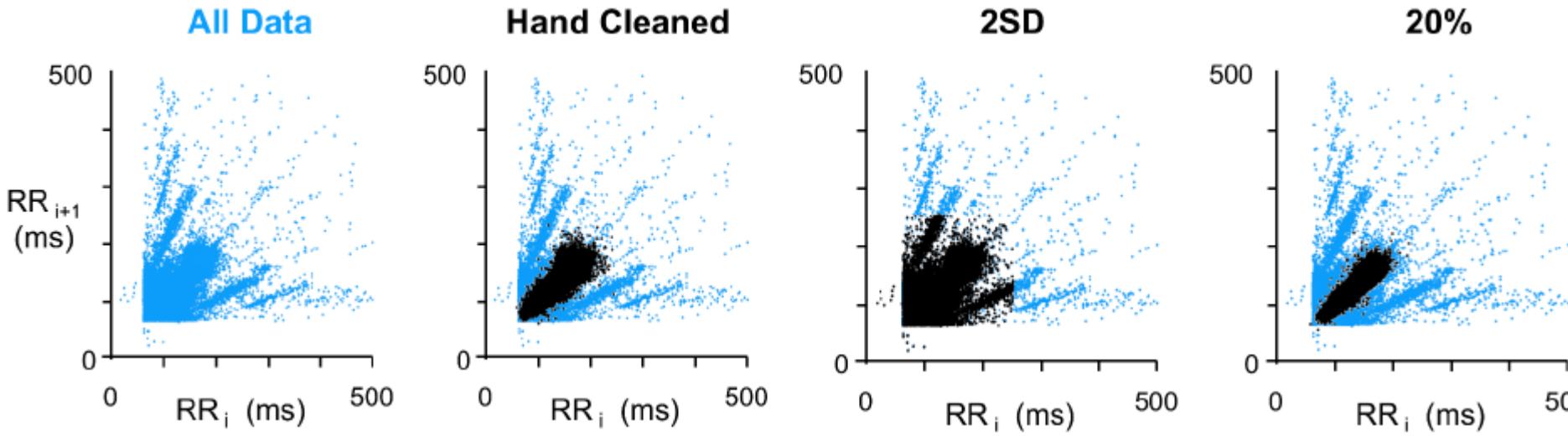


SDNN	Standard deviation (SD) of all normal-to-normal RR intervals (NN)
CV%	$100 \times SDNN/RR_{mean}$
SDANN	SD of averages of normal RR intervals in all 2 min segments
SDNNIDX	Mean of SD of normal RR intervals in all 2 min segments
rMSSD	SD of differences between adjacent normal RR intervals

Courtesy of Dr E Karey

SBNN=para+sympathetic+hormonal system
SDANN/SDNNIDX=para+sympathetic
rMSSD=parasympathetic

Methods of cleaning data HRV



	SDNN	SDANN	SDNNIDX	rMSSD
All Data	66.44	14.07	24.63	87.93
Hand Cleaned	**16.36**	**14.01**	**9.06**	**6.39**
2 SD	17.62	13.92	11.21	11.53
20% cut off	15.80	13.91	8.94	5.89

Courtesy of Dr E Karey

Arterial Carotid Artery Intima Medial Thickness

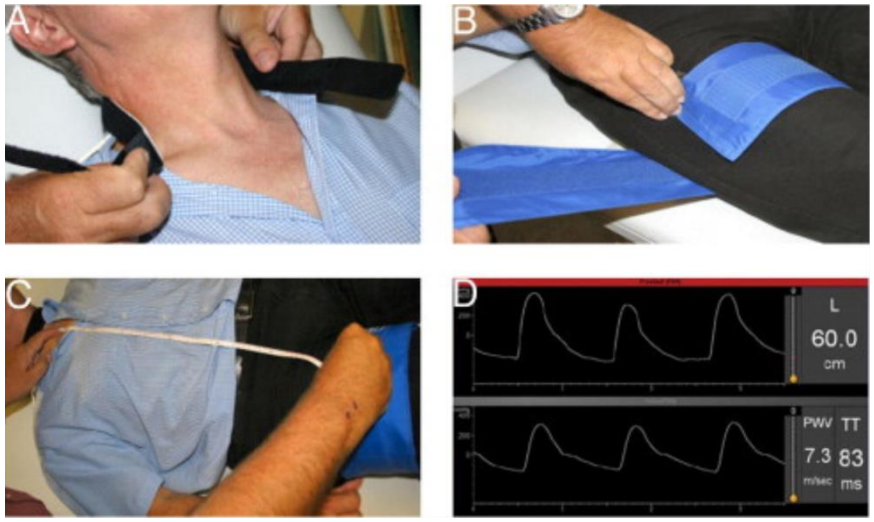
Arterial Carotid Artery Intimal Medial Thickness

- Arteries througout the body can be examined by ultrasound
- Allows visualisation and measurement of the lumen and the wall structure
- Carotid artery often used to represent systemic and cerebral circulation
- Identify arterial disease especially atheroma deposition
- Varies by gender, age, ethnicity, BMI, lipid levels hypertension
- Prognostic significance carotid IMT >1.0

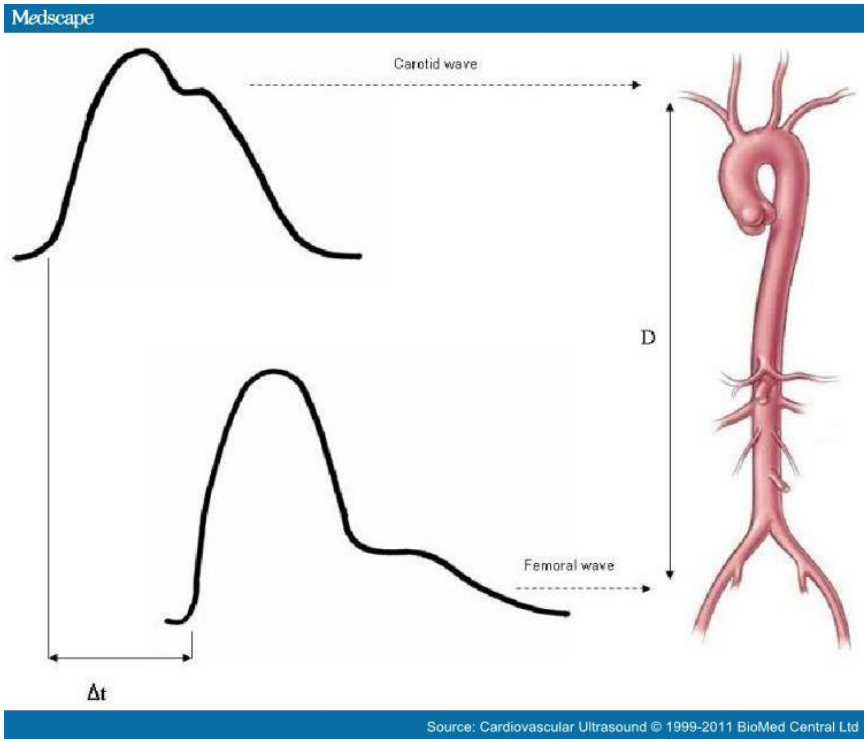
Pulse Wave Velocity

Pulse Wave Velocity

Cuffs over the carotid and femoral arteries



Speed of the pulse wave down the full aorta



PWV = Distance/Time

Distance = Carotid - femoral distance

Time = Lag between carotid & femoral waveforms

Arterial stiffness

Pulse Wave Velocity (PWV) is a measure of arterial (aortic) stiffness

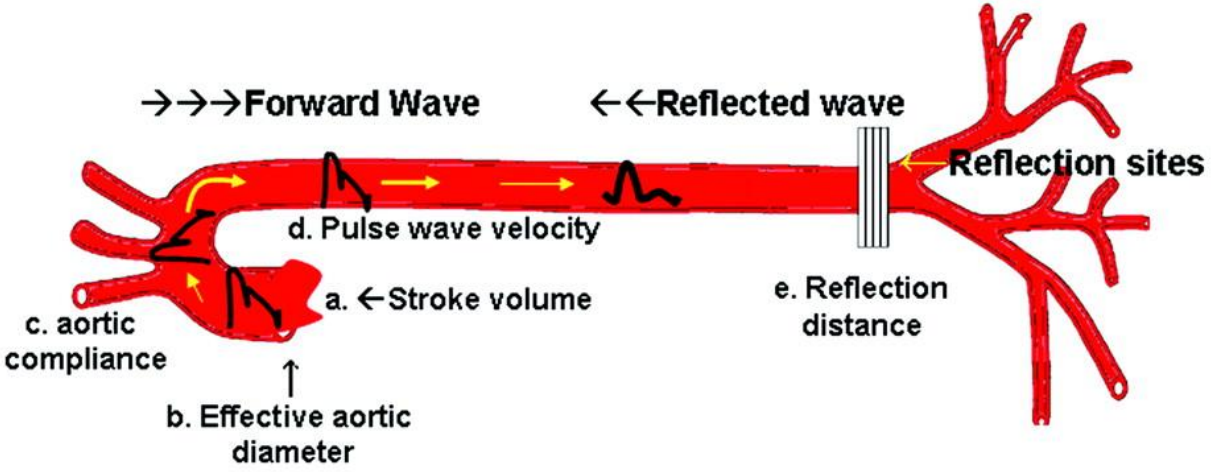
- Stiffness is the inverse of compliance (ΔDiameter/Δ Pressure)
- Higher PWV = stiffer arteries

Large arteries buffer pressure changes from ventricular contraction

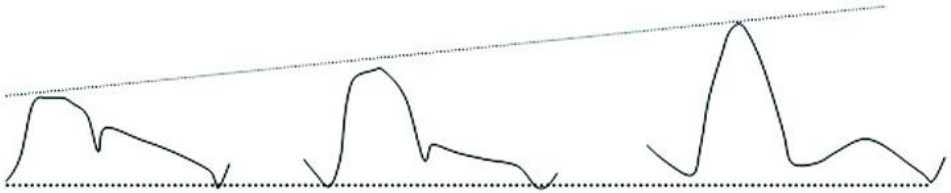
- Windkessel effect

Pulse Wave Velocity

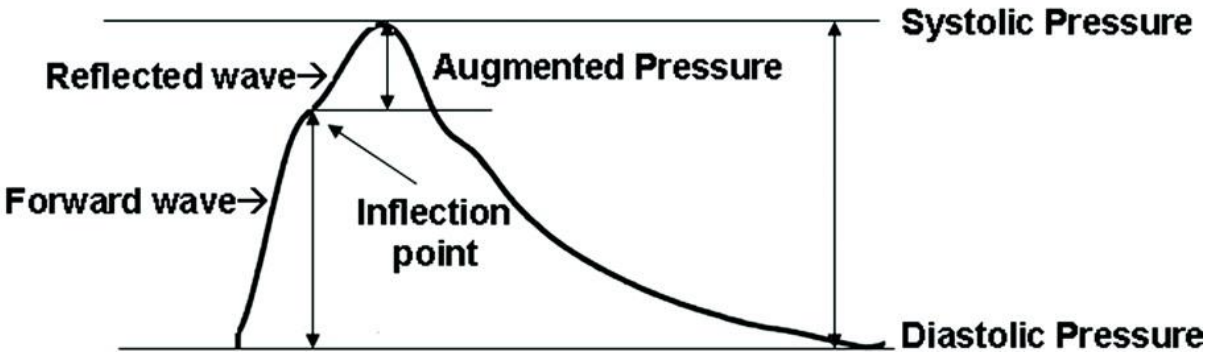
I. Correlates of Pulse Pressure



II. Peripheral Amplification of Pulse Wave



III. Summated Forward & Reflected Waves in the setting of a stiff aorta



Pulmonary function

Pulmonary function

- Essential to life, development and health
- Controls gas exchange and acid:base balance

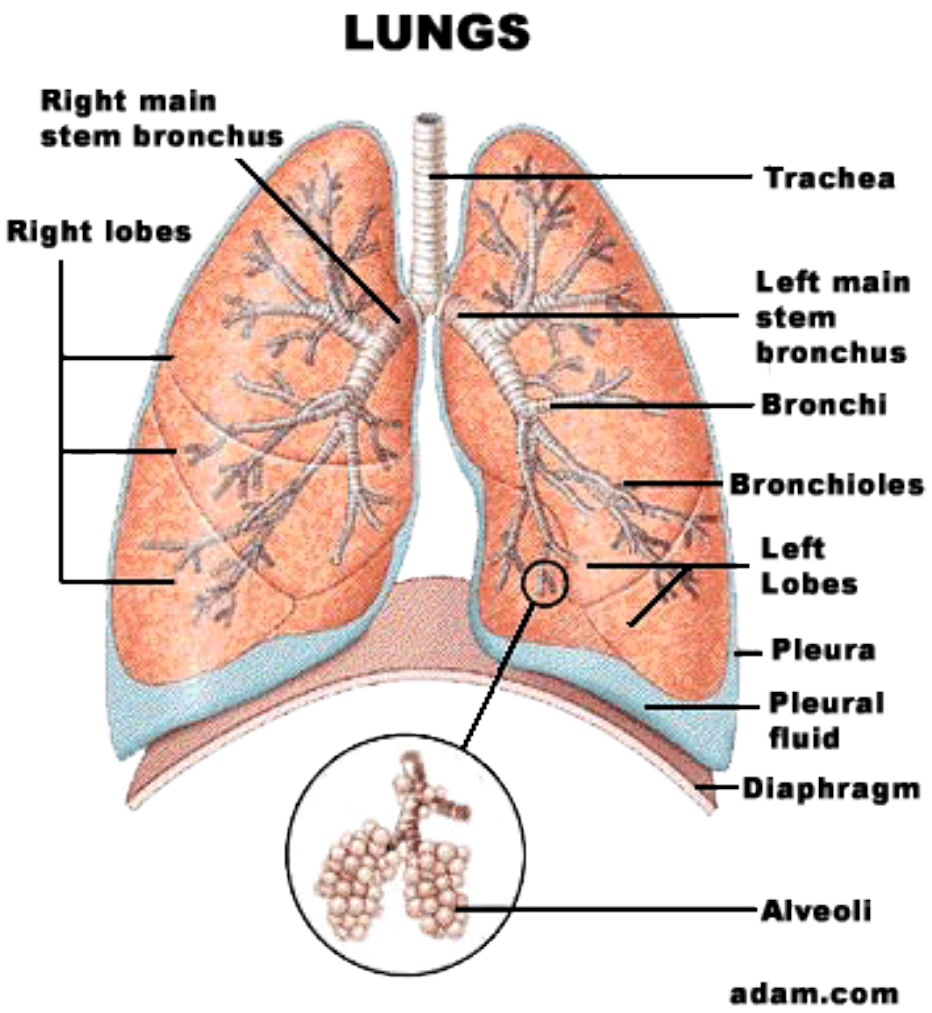


Image Jalal Deen and Ganesan International Journal of Applied Engineering Research ISSN 0973-4562 Volume 9, Number 22 (2014) pp. 17327-17343

Pulmonary function test

- Human physiology focuses on lung volumes and capacities
- Variation in healthy humans by age, gender, height and fitness
- Also affected by posture, pregnancy and chest wall muscle strength
- In disease predictable changes for classes of condition example COPD

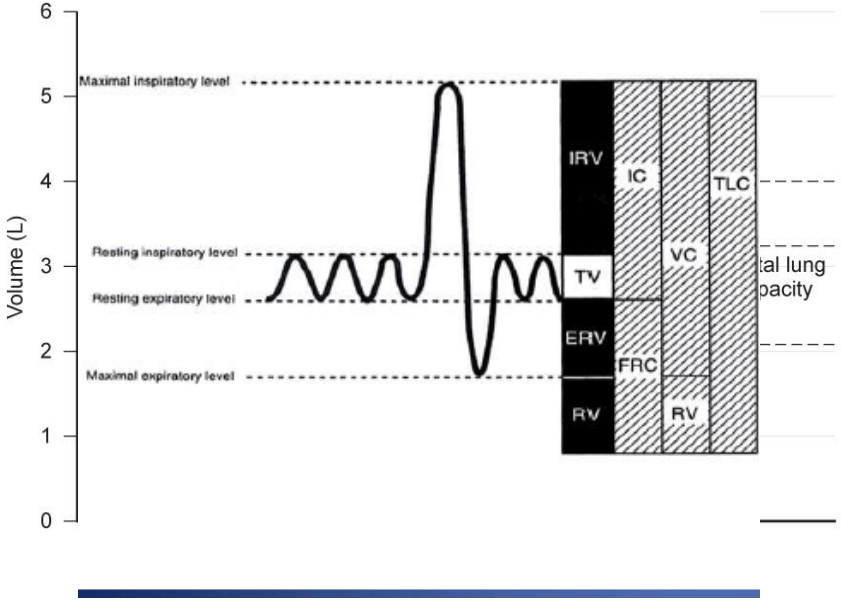


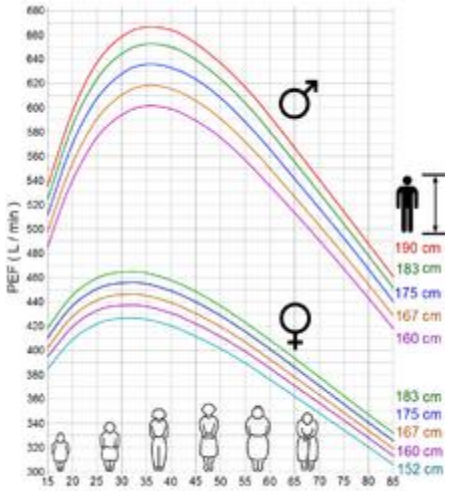
Image rom Ravindra Jha 2019

Measurements available

- Pulmonary Function tests are dynamic lung volumes
- Peak expiratory flow rate (PEFR)
- Spirometry
- Exercise capacity such as walk tests (but consider multi factorial)

Peak expiratory flow rate

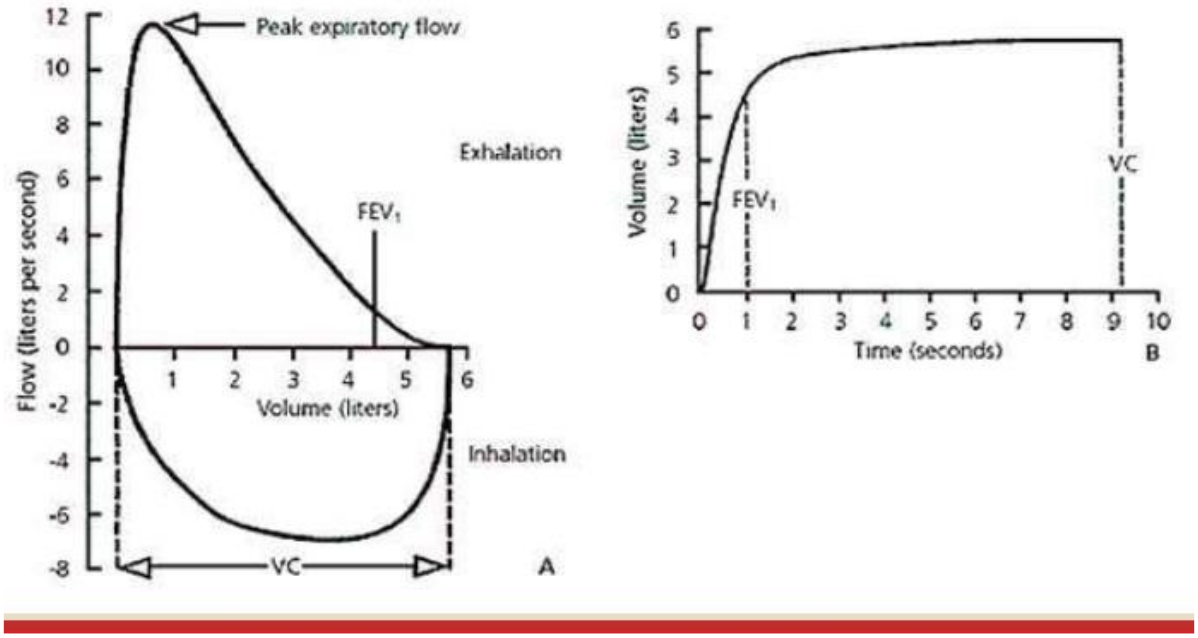
- Simple hand held device
- Measures airway calibre
- Measures the maximum expiratory flow rate ml/min
- Requires individual to engage with test maximal exertion



Spirometry

- Measures the volume of air an individual can inhale and exhale as a function of time
- Vital capacity
- Forced Vital capacity
- Forced expiratory volume 1 second
- PEFR
- Best of 3 measures in standard conditions

Spirometry



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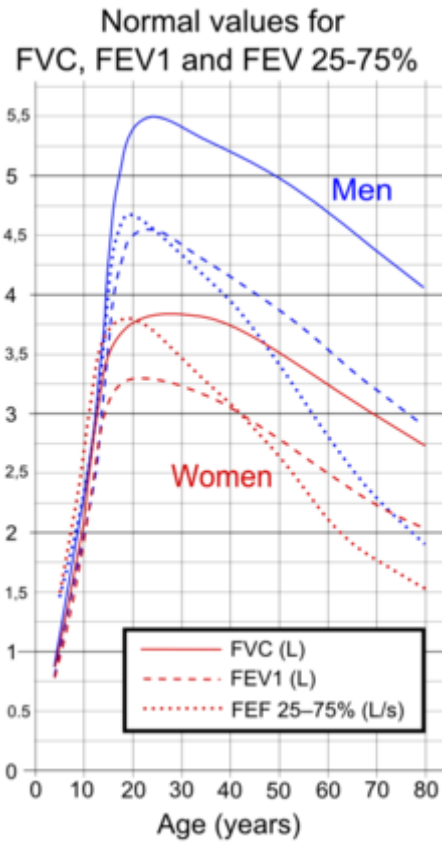
Spirometry

- Most used values are FEV1 and FVC
- Both assessed against predicted values
- FVC 80-120% normal; 70-79% mild reduction; 50-69% moderate reduction; <50% severe reduction
- FEV1 >75% normal; 60-75% mild obstruction; 50-59% moderate obstruction; <49% severe obstruction
- Also FEV1/FVC is .8 or higher normal if .79 or lower abnormal



Spirometry

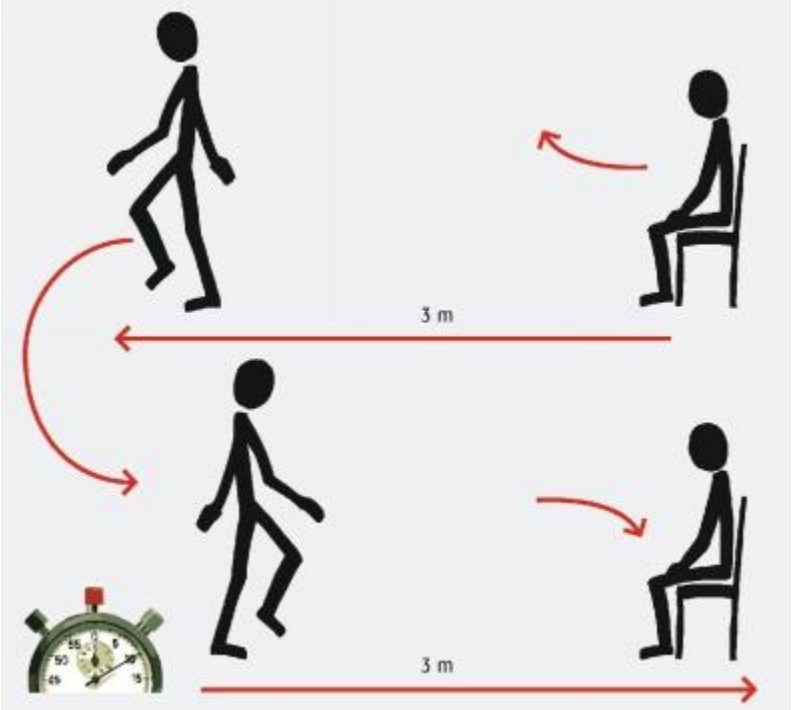
Disease states	FVC	FEV1	FEV1/FVC
Obstruction	Normal	Reduced	Reduced
Stiff lungs	Reduced	Reduced	Normal
Weak chest muscles	Reduced	Reduced	Normal

Human Performance Measures

Timed Up and Go test(TUG)

Timed Up and Go test(TUG)

- Widely used mobility test
- Transfers, gait, neuromuscular mobility
- Stand from a chair (standard height), walk 3m; turn around and walk back (can use aids but this reduces sensitivity balance element)
- Completed multiple times (best 2-4) with one treated as trial (unused)



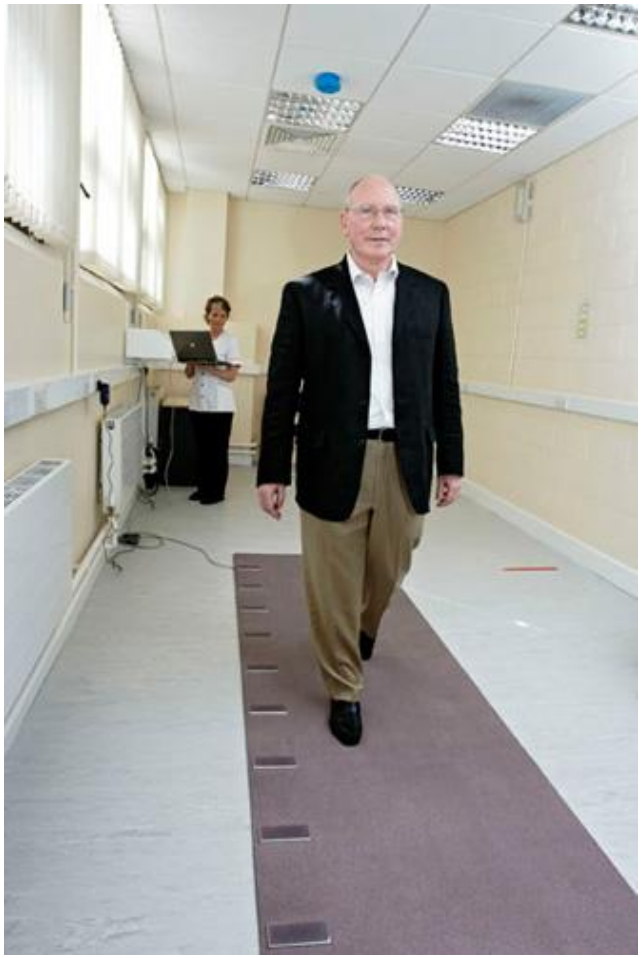
Timed Up and Go test(TUG)

- Content validity agreed by expert consensus
- Concurrent validity: Berg Balance Scale=0.81 Bartel Index =0.79
- Reliability (ICC)
- Interrater=0.98
- Intrarater =0.96
- O'Sullivan and Schmitz 2007
- Good correlation with Berg Balance Scale r=0.81(Cattaneo et a, 2006)
- Clinical cut offs between 11-13.5 seconds (Schoene et al, 2013)
- Cut off >13 seconds and % fallers prediction (Kisner et al 2012); sensitivity and specificity 87%

Walk speed

Walk speed

- Used widely as measure of muscle strength, physical performance and frailty
- Simple minimal equipment
- Methods vary measurement; different distances (3-30ms); additional actions (whether turn); number trials (2-4)



Walk speed

- Bohannon Age and Ageing 1997
- Reliability by reproducibility maximal and comfortable walk speed r>0.9
- Concurrent validity variety muscle strengths comfortable pace (r=0.19-0.25) maximum pace (r=0.29-0.56)

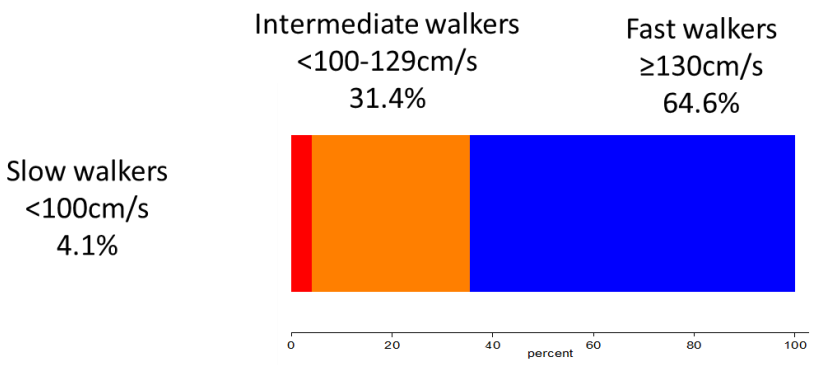
Table 4. Mean (X) and standard deviation (s) of comfortable and maximum gait speed presented by sex and decade of age

	Comfortable gait speed (cm/s)				Maximum gait speed (cm/s)			
	Actual		Height-normalized[a]		Actual		Height-normalized[a]	
Sex/decade	X	s	X	s	X	s	X	s
Men								
20s	139.3	15.3	0.788	0.093	253.3	29.1	1.431	0.162
30s	145.8	9.4	0.828	0.052	245.6	31.5	1.396	0.177
40s	146.2	16.4	0.829	0.090	246.2	36.3	1.395	0.197
50s	139.3	22.9	0.794	0.119	206.9	44.8	1.182	0.259
60s	135.9	20.5	0.777	0.116	193.3	36.4	1.104	0.198
70s	133.0	19.6	0.762	0.105	207.9	36.3	1.192	0.201
Women								
20s	140.7	17.5	0.856	0.098	246.7	25.3	1.502	0.142
30s	141.5	12.7	0.864	0.087	234.2	34.4	1.428	0.206
40s	139.1	15.8	0.856	0.098	212.3	27.5	1.304	0.160
50s	139.5	15.1	0.863	0.104	201.0	25.8	1.243	0.158
60s	129.6	21.3	0.808	0.131	177.4	25.4	1.107	0.157
70s	127.2	21.1	0.807	0.131	174.9	28.1	1.110	0.176

[a] actual speed (cm/s)/height (cm).

Walk speed

- Walk speed associated with variety of adverse outcomes
- Lifespan
- Cardiovascular disease outcomes
- Risk dementia
- Walking speed groups defined based on risk of adverse outcomes (Verghese et al 2011)



Chair stands test

- Used as test of leg strength, balance and stamina
- Protocols can be timed maximum number (30 seconds) or time taken to complete number of stands (5 or 10)
- Armless chair and hand positioning
- Associated with falls, disease and community lifespan

Image Hellmers et al Sensors 2019, 19, 1370; doi:10.3390/s19061370

Chair stands test

- Time to 5 stands Bohannon et al 2007
- Reliability test re test ICC=0.95
- Concurrent validity Lord et al 2002 against knee flexion/extension isometric force r=0.43
- Normative data 5 repitition from Bohannon et al 2015

Age (n)	Mean ± SD (95% CI)	Min-Max
14–19 (25)	6.5 ± 1.2 (6.0–7.0)	4.7–9.7
20–29 (36)	6.0 ± 1.4 (5.6–6.5)	3.9–11.2
30–39 (22)	6.1 ± 1.4 (5.5–6.8)	4.1–10.4
40–49 (15)	7.6 ± 1.8 (6.6–8.6)	5.6–13.2
50–59 (20)	7.7 ± 2.6 (6.5–8.9)	4.2–12.1
60–69 (25)	7.8 ± 2.4 (6.8–8.7)	4.7–15.1
70–79 (24)	9.3 ± 2.1 (8.4–10.1)	5.5–13.3
80–85 (14)	10.8 ± 2.6 (9.3–12.3)	5.8–17.6
14–85 (181)	7.5 ± 2.4 (7.1–7.8)	3.9–17.6
50–85 (83)	8.7 ± 2.6 (8.1–9.3)	4.2–17.6

Physical activity

Physical activity

- Definition: any bodily activity by skeletal muscles resulting in an increased energy expenditure
- Sedentary defined as any waking behaviour characterised by MET <1.5 sitting or reclining
- Inactivity defined at performing insufficient amounts of Moderate to Vigorous PA (compared to guidelines)

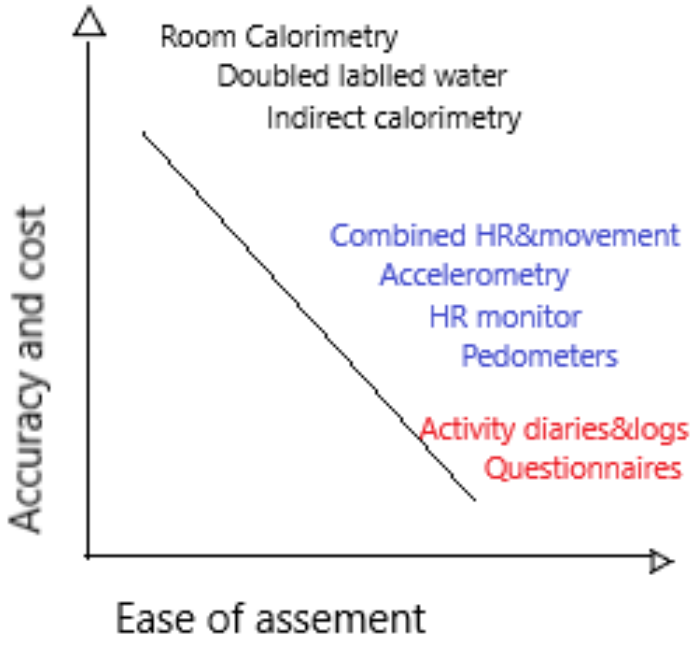
Physical activity a complex behaviour

- Type
- Domain or location
- Frequency
- Duration
- Intensity or physiological effort
- Volume product of frequency, duration and intensity

Image from clipart library

Measuring Physical Activity Levels of Sophistication

- Trade off between accuracy and feasibility
- Criterion methods in black
- Monitor based in blue
- Report based in red
- Note first two are objective and red subjective



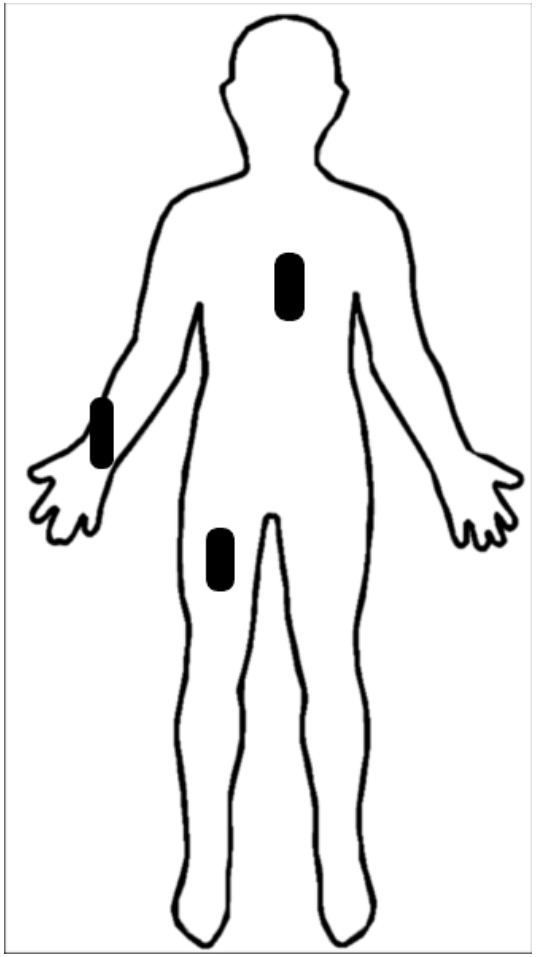
Physical Activity Questionnaires

- Systematic review 96 studies
- Reliability objective validity: accelerometers; Heart Rate; Pedometer; double label water
- Reliability by ICC 0.62-0.76
- Validity by r 0.3-0.41
- Old and new tools not difference

Helmerhorst et al IJBNPA 2012

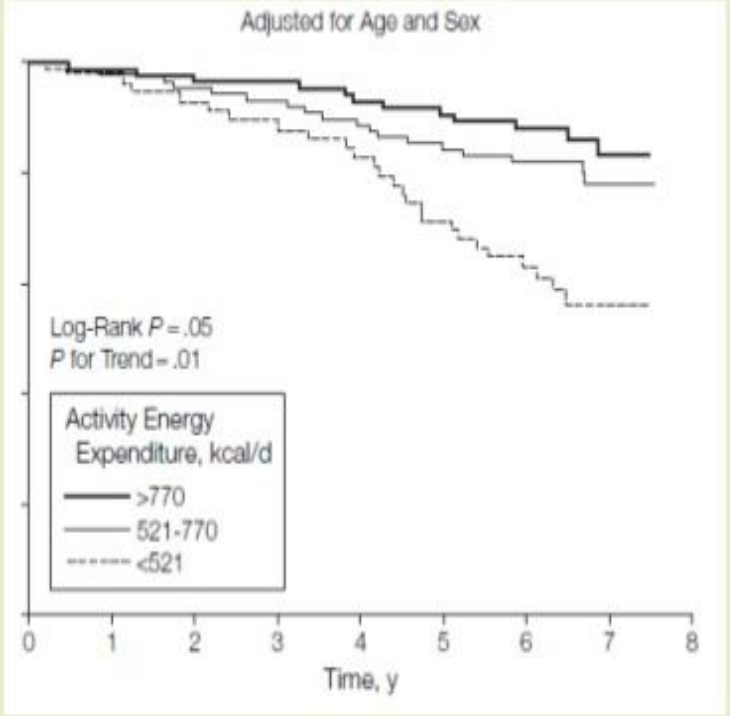
Physical Activity Objective Measures

- Methods use wearables
- Many devices many positions
- Heart rate (limitations elevation stress or environment)
- Accelerometer (cannot differentiate walking on flat or uphill or intensity of movement)
- Solution may be combination HR and Accelerometer



Physical Activity Objective Measures

Daily Activity Energy Expenditure and Mortality Among Older Adults



(Manini et al, JAMA 2006)

Grip strength

Grip strength measurement

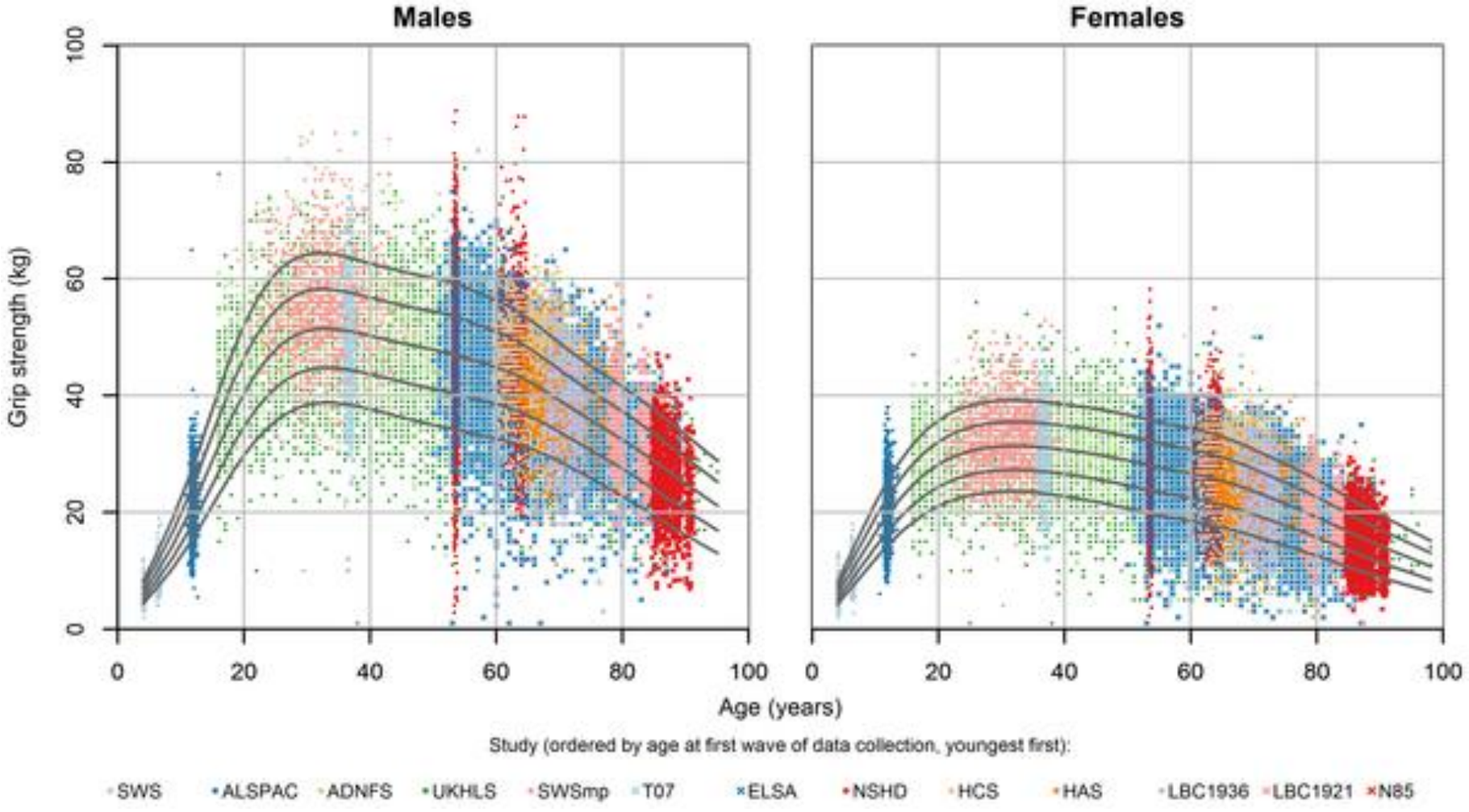
- Maximal hand grip strength (HGS) is method for assessing muscle strength and function
- Number of determinants including volition thus standardisation of methodology critical
- Image Instrument Takei Japan

Image from Wan Hafizi Wan Kamaludin and Hermizan Halihanafiah 2012

Grip strength measurement influences

- Hand dominance
- Gender
- Age
- Hand size
- Time of day/day of week
- Temperature
- Occupation
- Hand deformities/diseases
- Examiner/motivation

Figure 1. Cross-cohort centile curves for grip strength.



Dodds RM, Syddall HE, Cooper R, Benzeval M, Deary IJ, et al. (2014) Grip Strength across the Life Course: Normative Data from Twelve British Studies. PLOS ONE 9(12): e113637. https://doi.org/10.1371/journal.pone.0113637
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0113637

PLOS ONE
TENTH ANNIVERSARY

Acknowledgements

- Endocrine system hormones: presentation by Jay Swan 2011
- Kidney function tests: presentation by Tapeshwar Yadav 2016
- Body composition 720: presentation Fahmida Hashem 2015
- Anthropometry and Physical Characteristics in Man: presentation by Babakayode A Olagbaye 2017
- Anthropometry presentation bu Amerendra Singh 2013
- Body Composition Concept and Utility: presentation Majid Abi SaaB 2015
- Arterial blood pressure: presentation Mohamed Ababmeh and Lubna Abu Alrub 2015
- Blood pressure and its regulation: by Haristha Srinivasan 2018
- Blood pressure targets 2017 still strugling for the right answer: presentation Magdy El-Masry 2017
- Basics of the EKG: presentation by Ragwhender Singh 2008
- Utilizing Heart Rate Variability (HRV) for Preclinical Evaluation of Cardiovascular Function & Related Disease: presentation InsideScientific Emma Carey 2017
- Carotid Doppler Ultrasound Part 1: presentation by Muhammad Bin Zulfiqar 2013 and 2014
- Pulmonary Function Tests: presentation by Ravindra Jha 2019
- THE EVALUATION OF HAND GRIP STRENGTH AMONG BADMINTON AND TABLE TENNIS PLAYERS
- The evaluation of hand grip strengths among badminton and table tennis players: presentation by Wan Hafizi Wan Kamaludin and Hermizan Halihanafiah College of Allied Health Sciences Malaysia 2012
- TILDA research team