THE ROLE OF THE ANESTHESIOLOGIST IN MEDICAL DEVICE DEVELOPMENT: USE OF VASCULAR TONE AS CLINICAL EXAMPLE

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INTRODUCTION

- Medical device development follows a well established steps.
- Many of these steps overlap with each other as scientists invent, refine and test the device.
- **STEP 1: Device discovery and concept**
- Begins when researchers see an unmet medical need
- create the concept/idea of new device
- Determine if this concept is workable or not “build a proof of concept”: a document that outlines the steps

WHAT CLINICAL QUESTIONS NEED TO BE ANSWERED?

- Change in volume status and/or vascular tone are the most common reasons for hemodynamic impairment during mechanical ventilation
- Hypervolemia and Hypovolemia as well as hypotension due to prolonged vasodilation are associated with high morbidity and mortality.
- Determination of patient's volume status as well as vascular tone are of great clinical relevance in directing the appropriate therapeutic intervention either fluid vs. pressors or both.
- The goal will be to improve tissue perfusion (global vs. organ specific) and improve outcome.

(Rivers et al, N Eng J Med 2001)(Monk et al, Anesthesiology 2015)

WHAT AS A CLINICIAN WOULD YOU BE LOOKING FOR?

- Changes in vascular tone and compliance (using vasoconstrictors or vasodilators) could falsely suggest:
  - Normovolemic state when the patient is in fact hypovolemic
  - Hypovolemic state when the patient is in fact normovolemic.
  - failure to recognize this condition subjects patients to the known negative consequences of an iatrogenic positive fluid balance.
- Both sensitivity and specificity of PPV was decreased with changes in vascular tone
  - Norepinephrine could significantly reduce (PPV, SVV) and mask a true intravascular volume deficit possibly by changing vascular compliance and shifting blood from unstressed to stressed volume.
  - PPV amplification is similar in hypovolemia or pharmacologic vasodilation induced by sodium Nitroprusside (relative hypovolemia).

(Nouira et al, Crit Care Med 2005)(Westphal, Clinics 2010)(Hadian et al, J Crit Care 2011)

WHAT AS A CLINICIAN WOULD YOU BE LOOKING FOR?

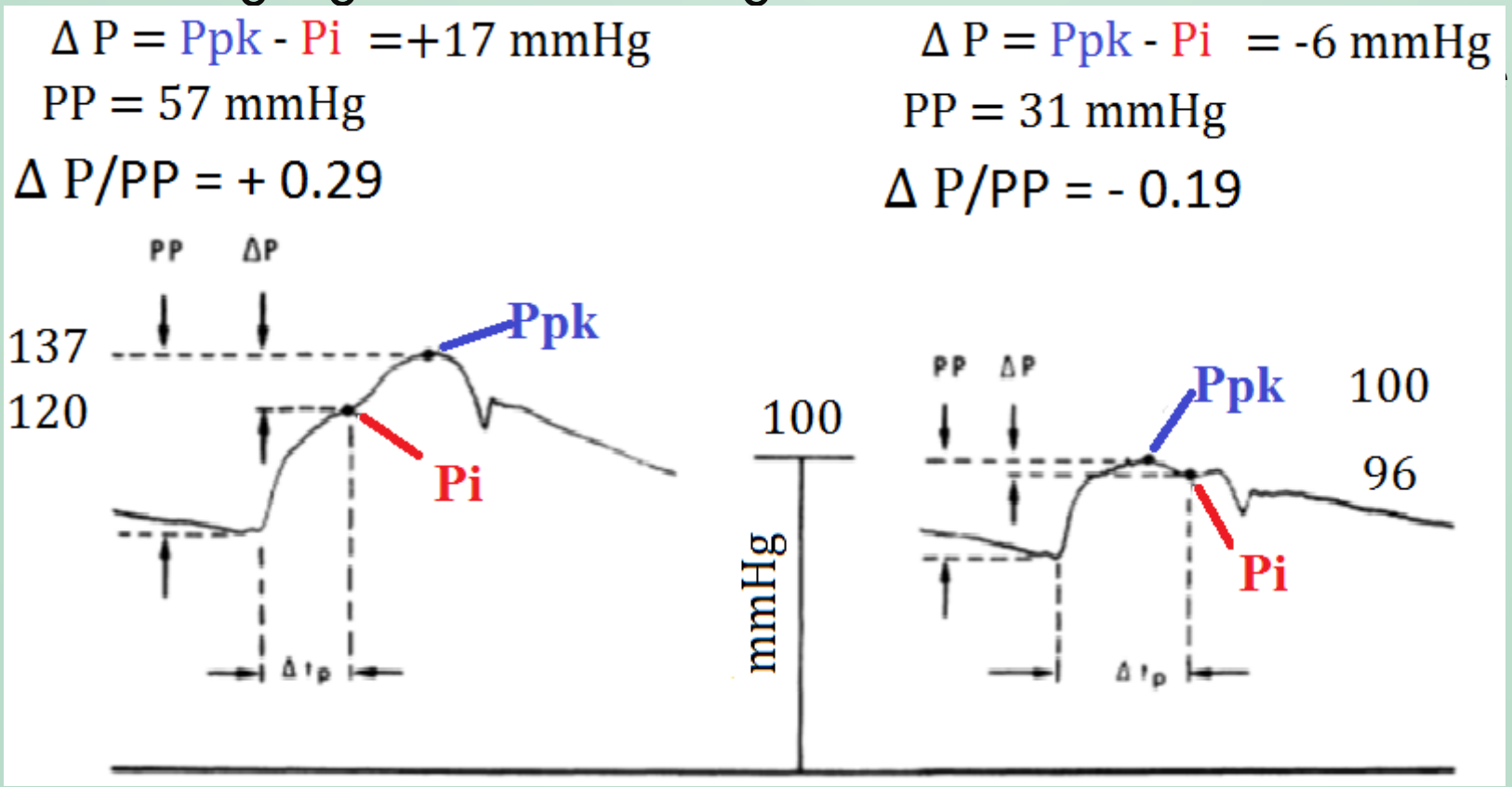
POSITION OF DN & BP;

- Hypotension and DN close to the baseline----most likely Vasodilation-----
  --need pressors
- Hypotension and DN close to the peak------most likely hypovolemic-------
  ----need volume

(Morikawa , Nature 1967)(Stengele et al, Eur J Clin Pharmacol 1996)

PARAMETERS RELATED TO SYSTEMIC VASCULAR IMPEDANCE

- The basic idea of the augmented index was first described by Murgo et al in 1980 in relation to the reflection return point in the ascending aorta.
- Kelley et al first used the term "augmentation index" in their 1989 study evaluating age-related changes in AIs.

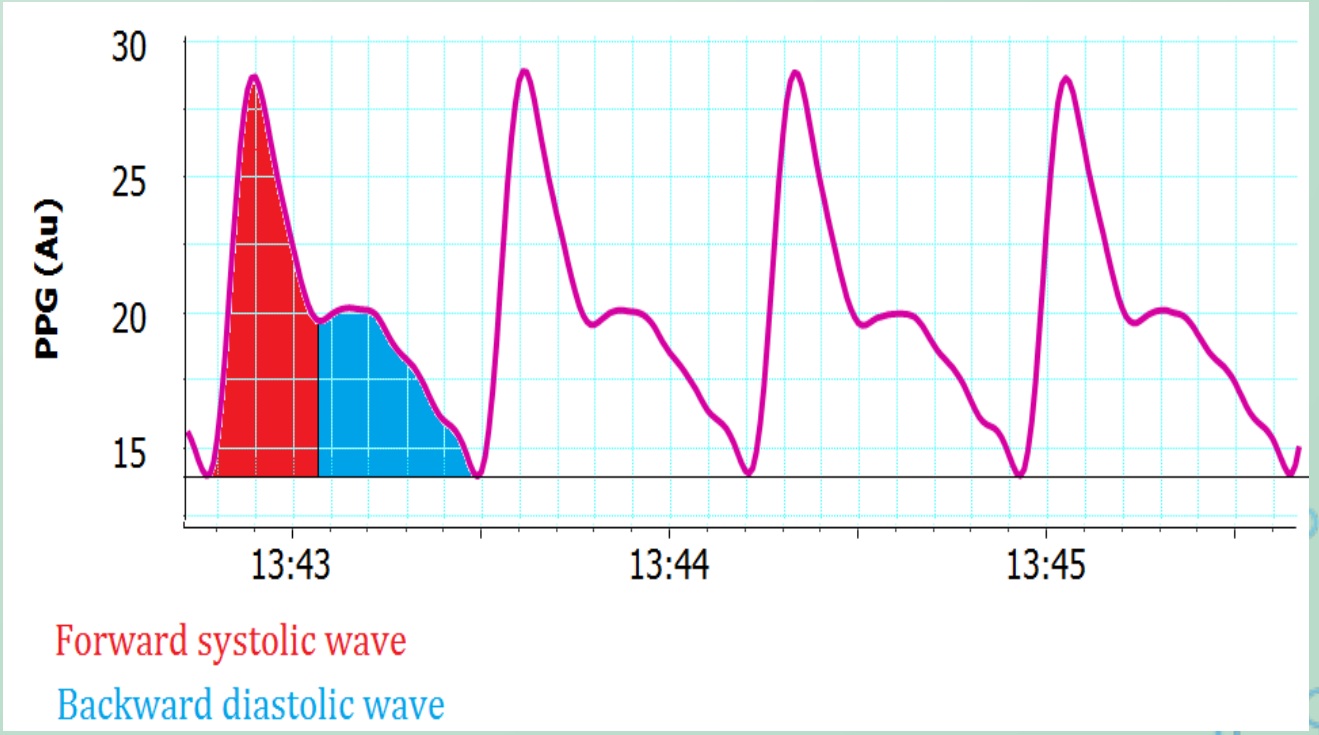


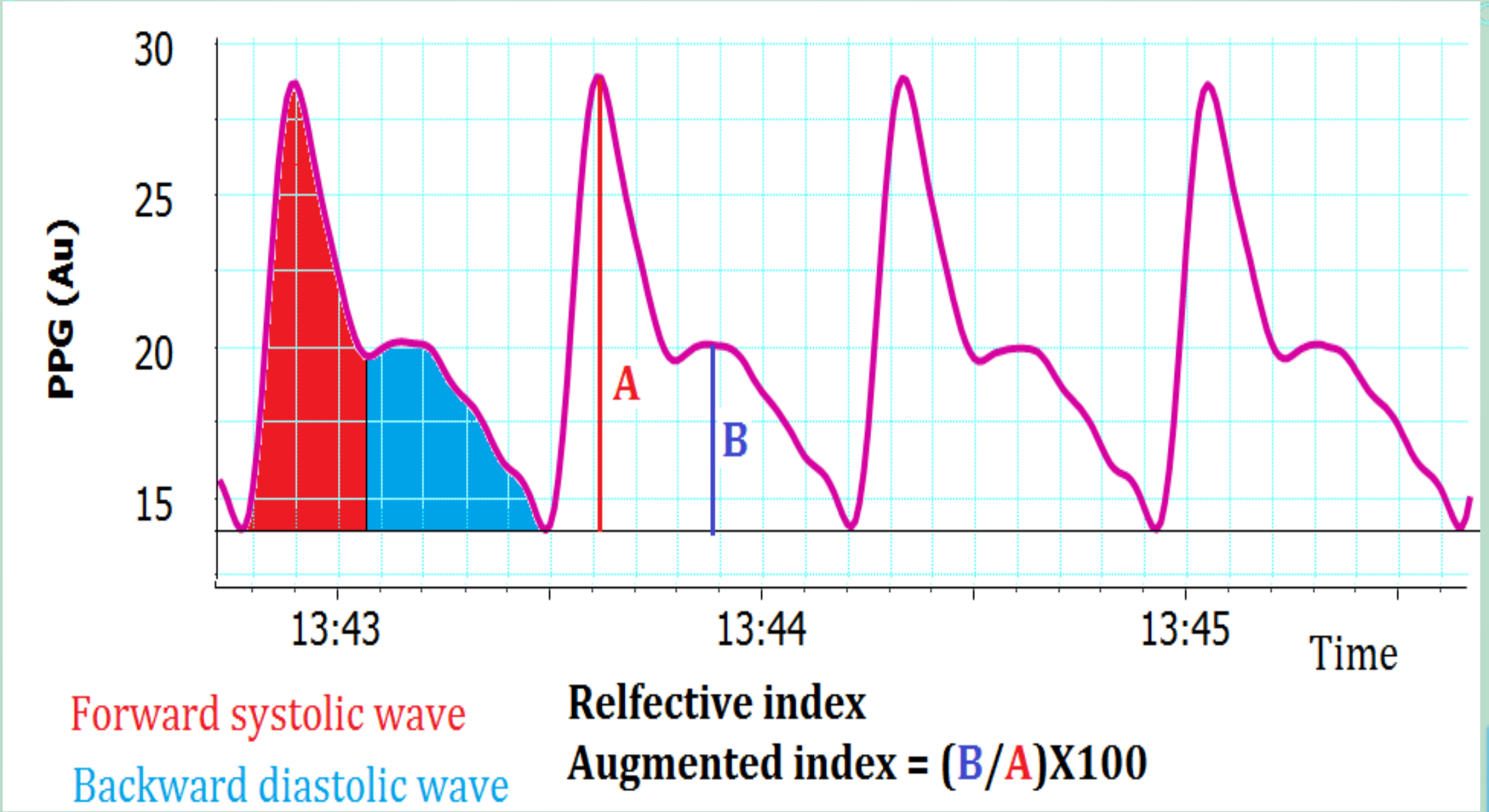
lley et al, Circ 1989)

- Photoplethysmography (PPG) represents the volume of blood versus time curve measured in a tissue during 1 cardiac cycle
- Similar to Pulse pressure waveform; PPG (volume) waveform has two components:

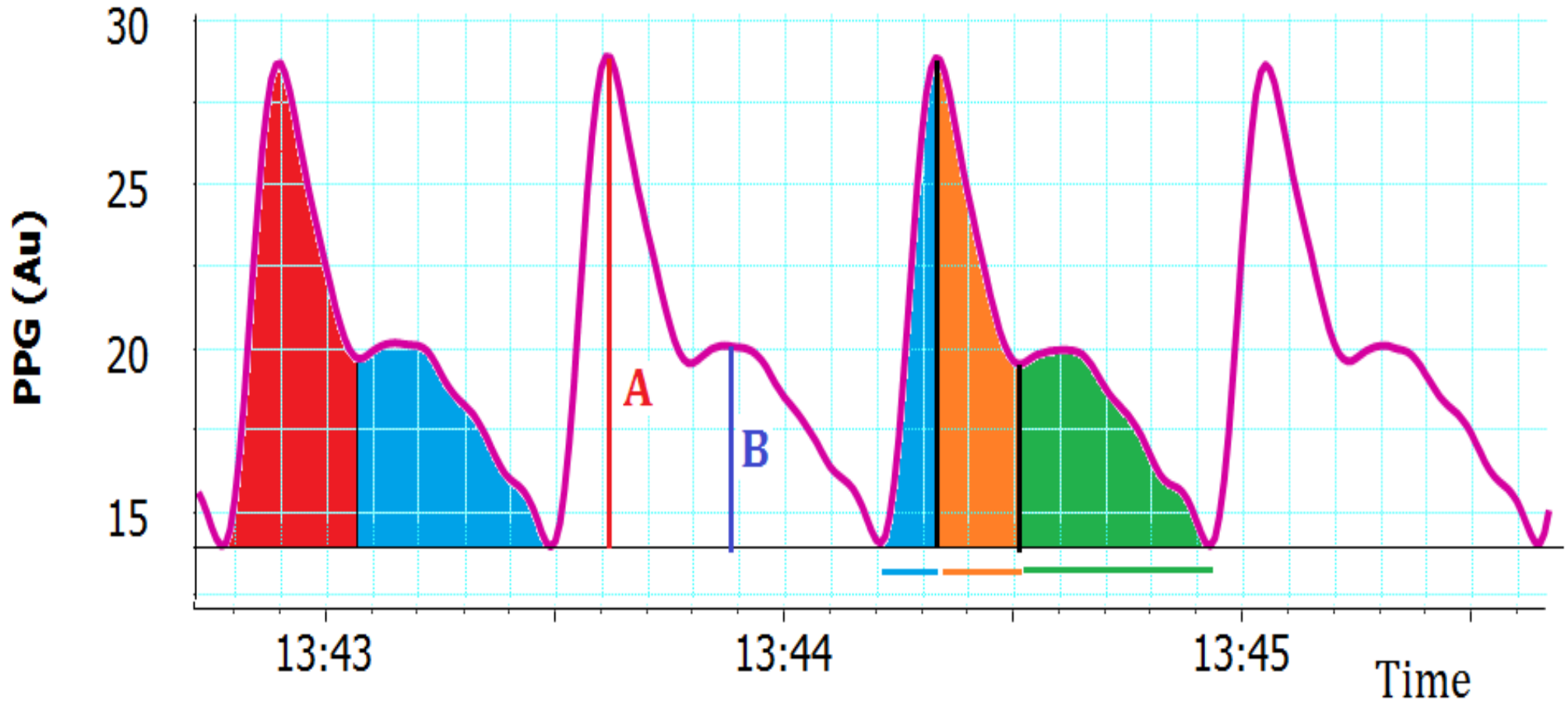
a systolic-forward: resulting from the direct pressure wave traveling from the left ventricle to the digit

a diastolic-backward: resulting from reflections of the pressure wave by arteries of the lower body back to the finger





(J Am Coll Cardiol 1999)(Measurement Sci Rev 2012)



Forward systolic wave

Backward diastolic wave

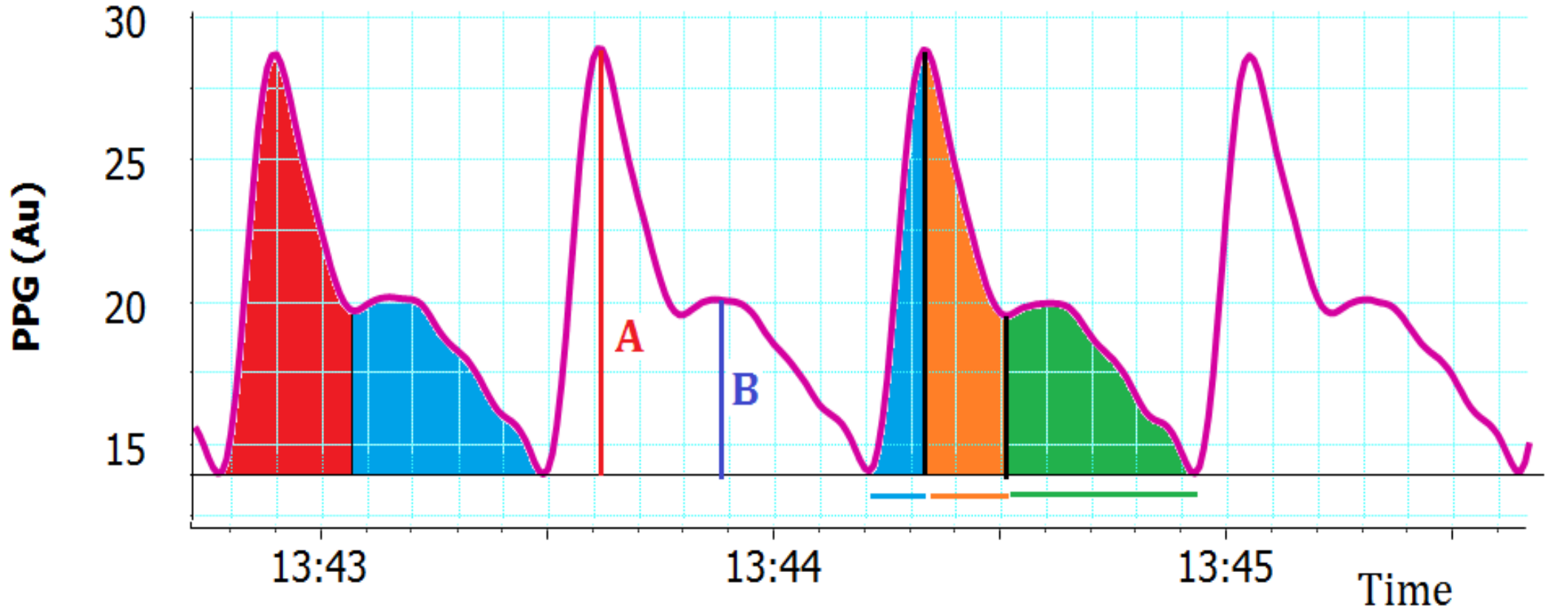
Relfective index

Augmented index = (B/A)X100

Time to Peak

Peak to peak time

DN-baseline time



Forward systolic wave

Backward diastolic wave

Relfective index

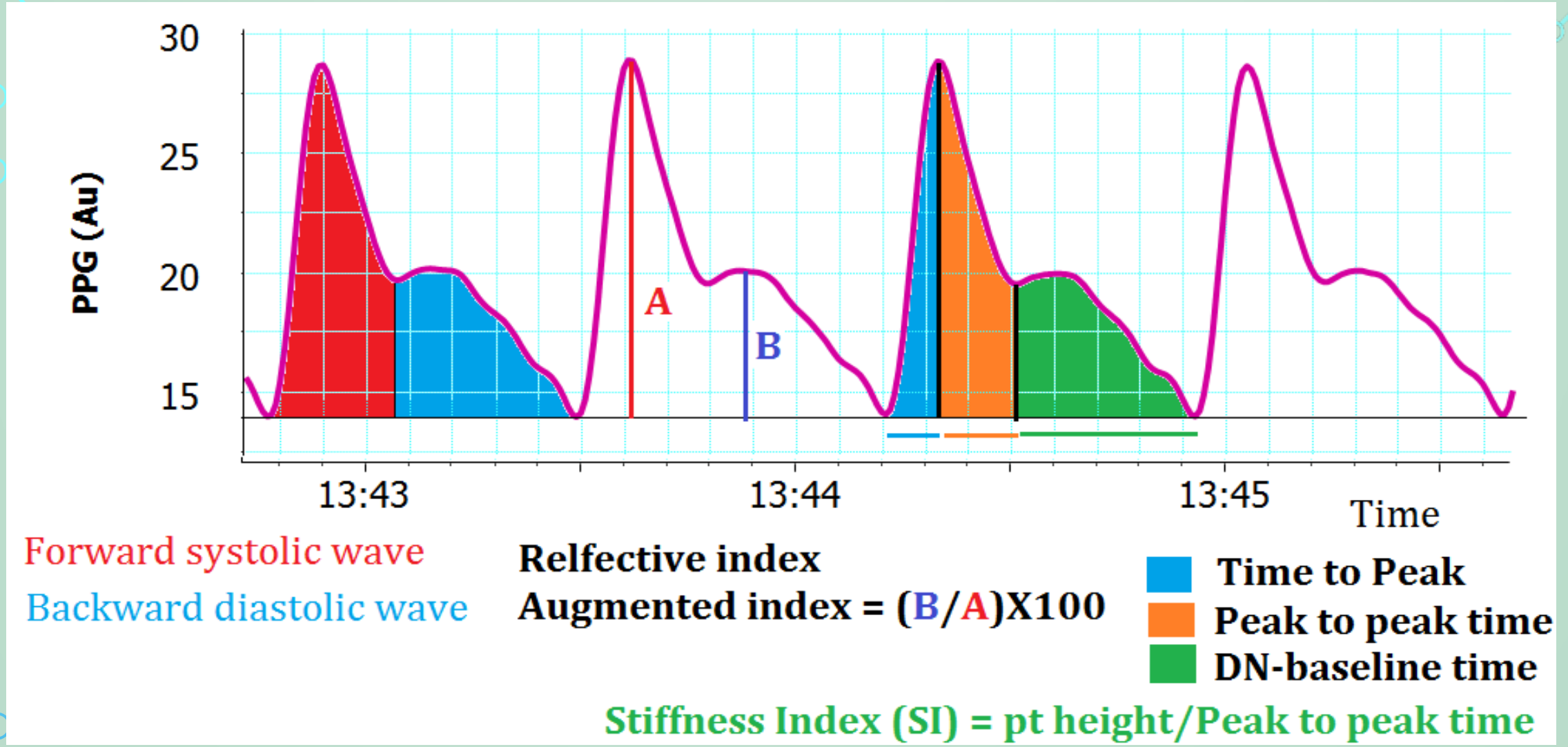
Augmented index = (B/A)X100

Time to Peak

Peak to peak time

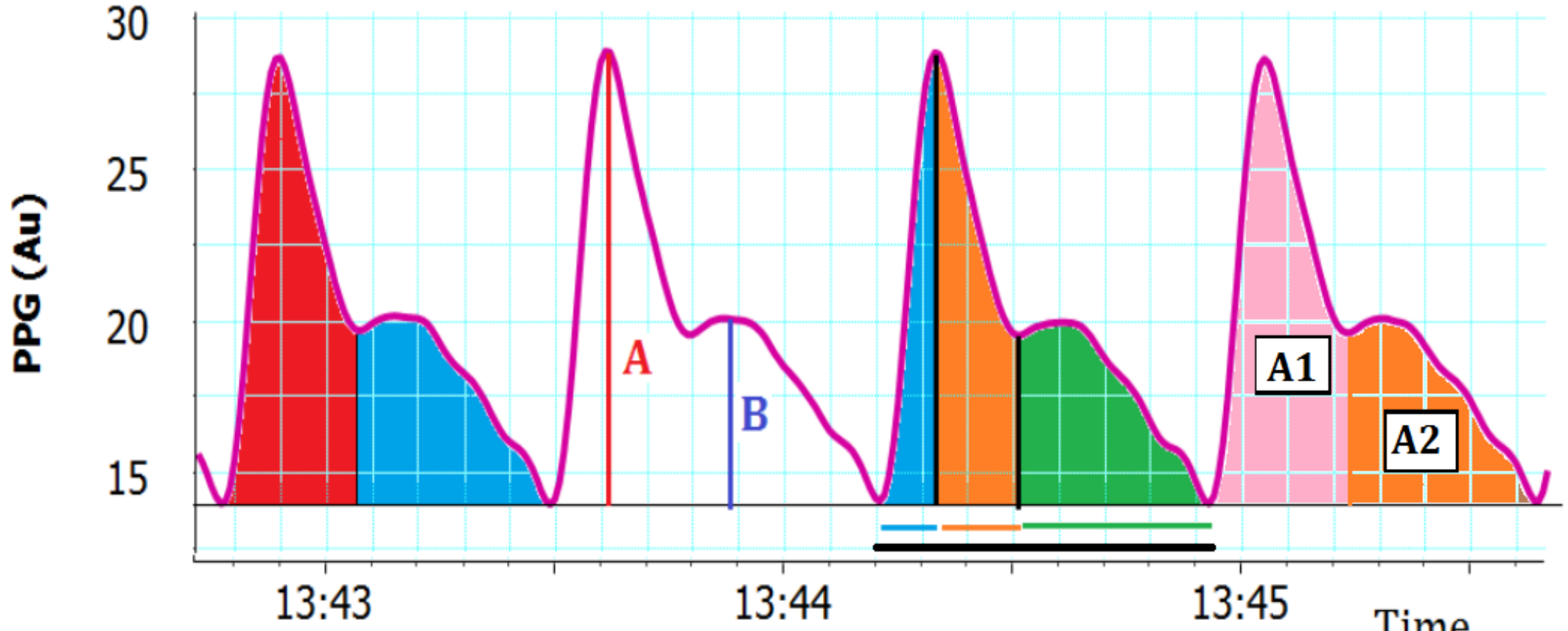
DN-baseline time

Stiffness Index (SI) = pt height/Peak to peak time



- SI is related to the chronological age and is related to vascular elasticity.
- highly predictive of outcome inpatients with cardiovascular disease

(Am J Epidemiol 1994)(Clin Sci 2002)



Forward systolic wave

Backward diastolic wave

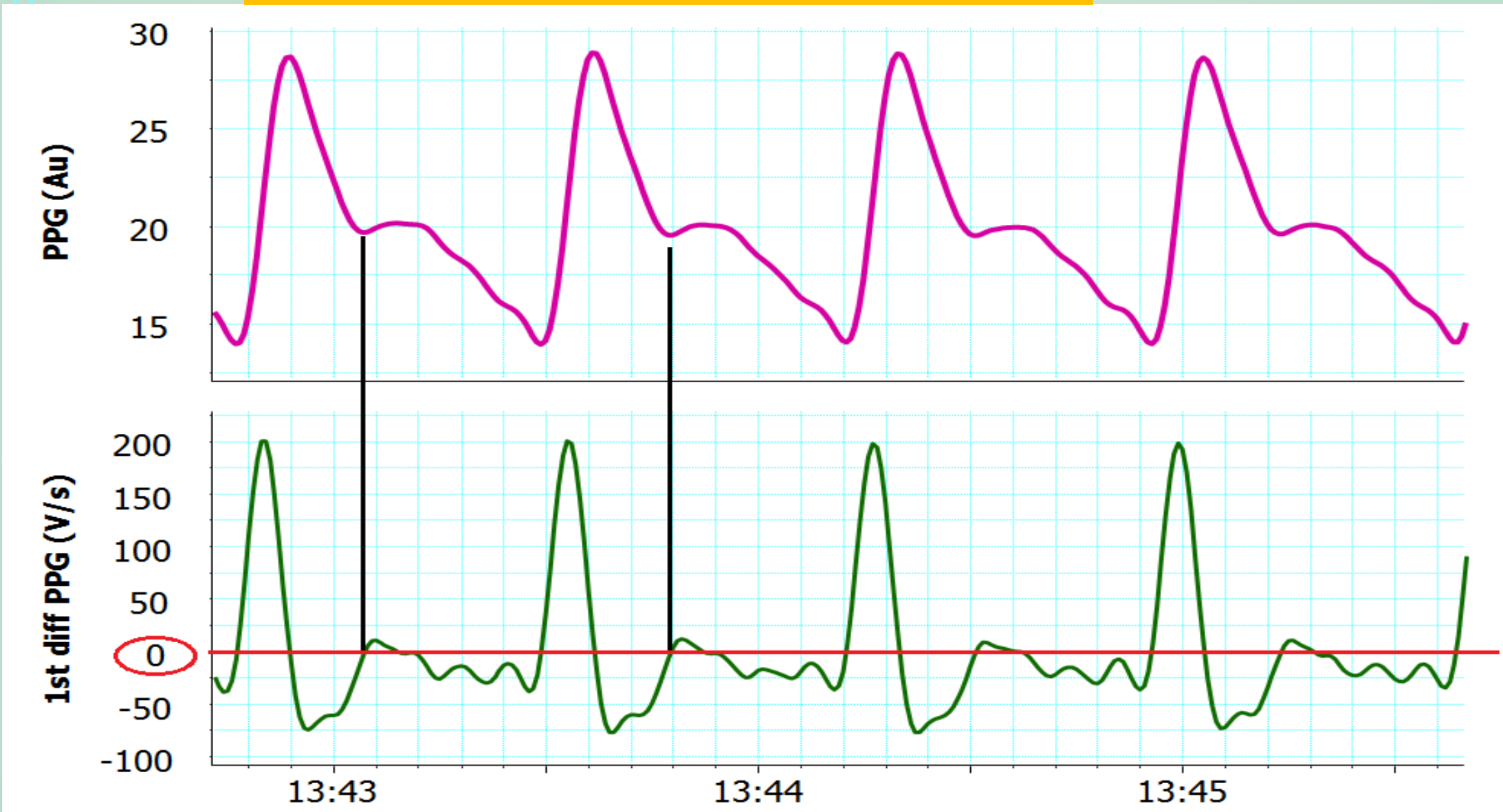
Relfective index or Augmented index = (B/A)X100

Stiffness Index (SI) = pt height/Peak to peak time

Pulse area ratio = A2/A1

- **Time to Peak**
- **Peak to peak time**
- **DN-baseline time**
- **Total time**

How to identify the Dicrotic Notch??



INTRODUCTION

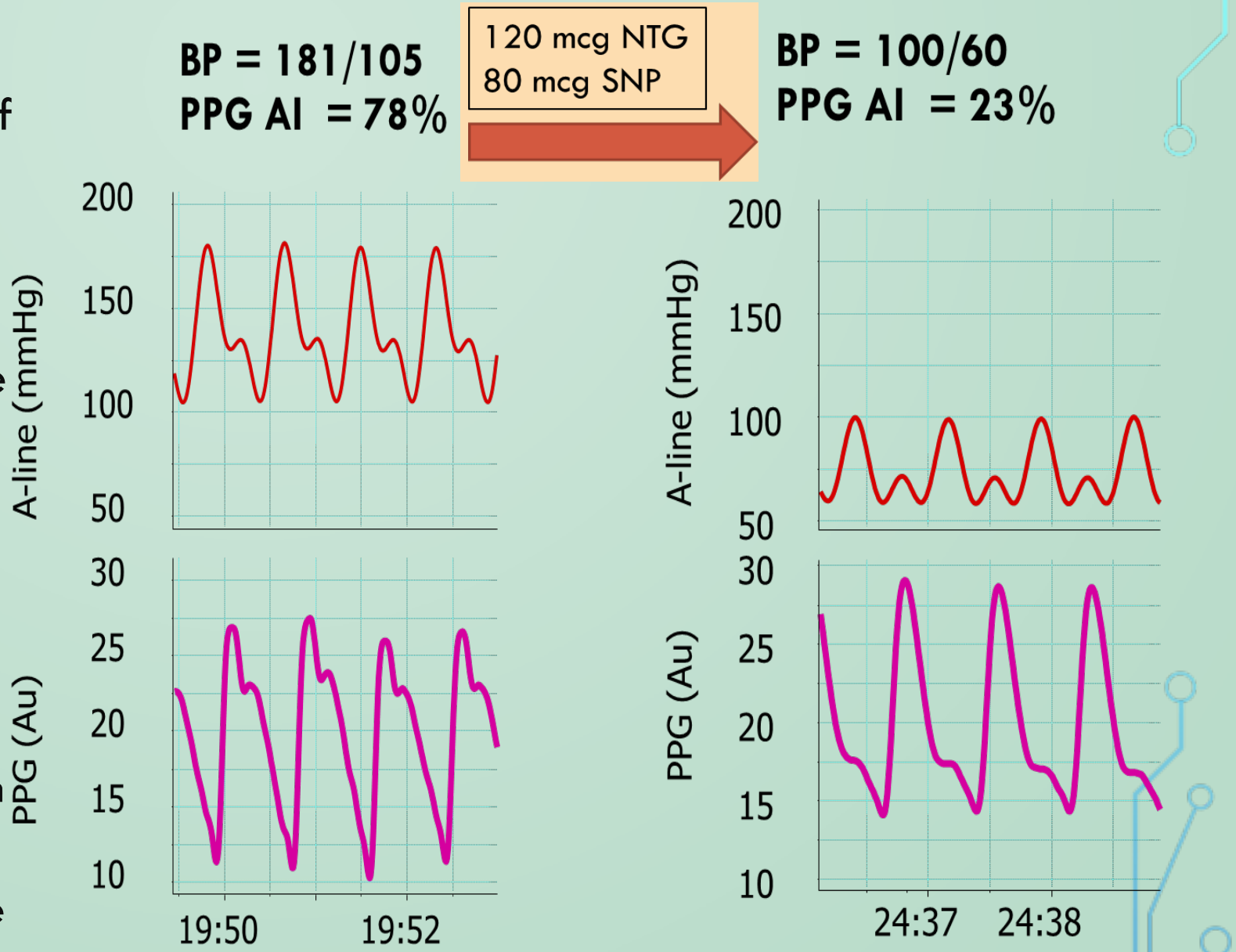
- Medical device development follows a well established steps.
- Many of these steps overlap with each other as scientists invent, refine and test the device.
- **STEP 1: Device discovery and concept**
- **STEP 2: Preclinical research prototype device**
- If the concept is practical----Researcher build a device prototype (early version of the medical device)
- Researcher use this prototype device to refine, test and improve the clinical findings as well as reduce potential risk of harm to people.

THE CLINICAL VALUE OF THESE INDICES

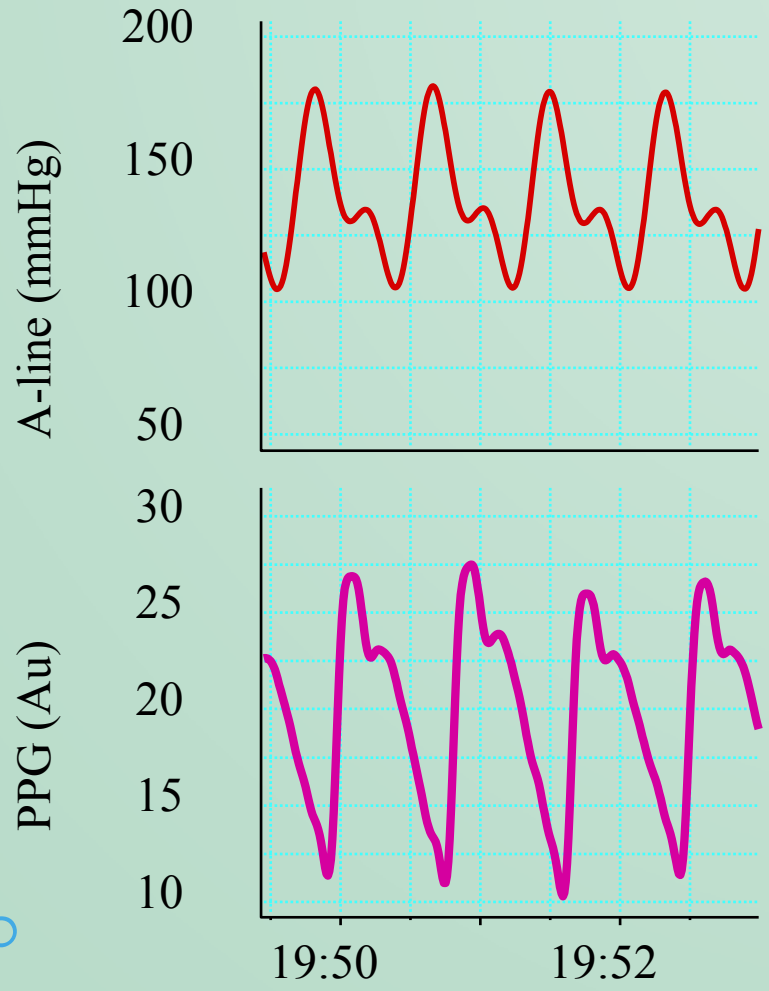
- RI can provide a window to vascular age and arterial compliance.
- The amplitude of the reflected wave increases as large arteries stiffen with age or disease processes
- SI is related to the chronological age and is related to vascular elasticity.
- Stiffness index (SI) is a measure of larger artery stiffness, surrogate measure of PWV
- SI has highly predictive of outcome in patients with cardiovascular disease
- As age advance, arteriosclerosis increased this will lead to:
  - diastolic peak tends to be closer to systolic peak
  - reduces peak to peak time
  - increased SI
  - higher RI
  - decreased arterial compliance

MONITORING OF CHANGES IN ARTERIAL VASCULAR IMPEDANCE

- **Vasoconstriction----**stiffer vascular tree---- faster return of the pulse wave to the LV early in systole----Increasing LV outflow impedance, dicrotic notch position moves toward the left into the systolic wave.
- **Vasodilator therapy----** dilation of small arteries ----- reducing wave reflection from the lower body----slow return in the pulse wave to the LV----- reduction in LV outflow impedance, dicrotic notch position close to the baseline

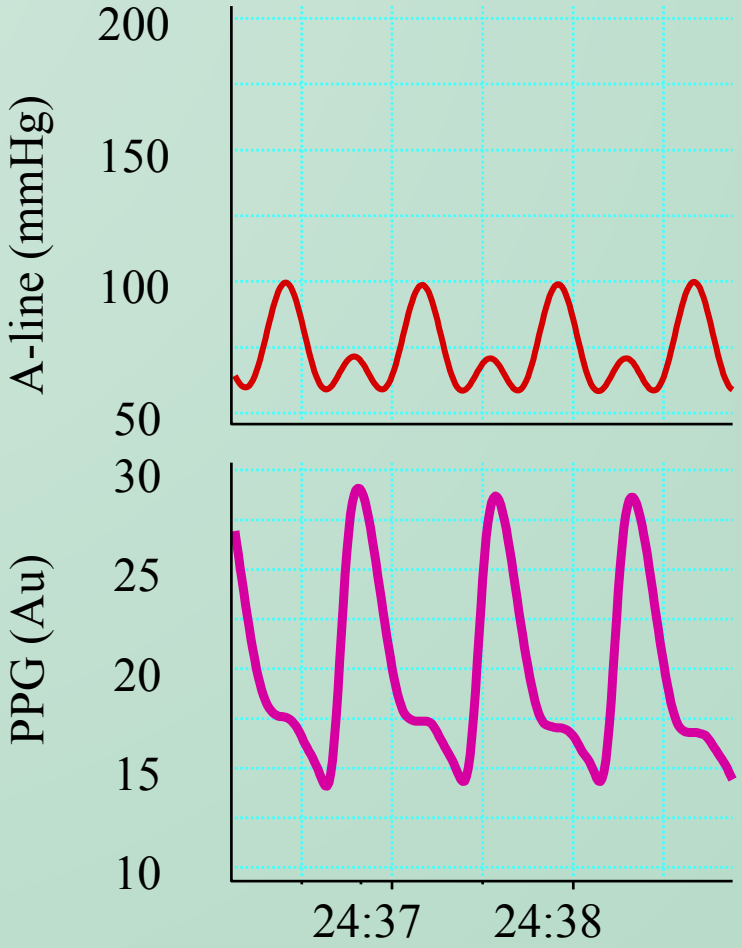


BP = 181/105
PPG AI = 78%



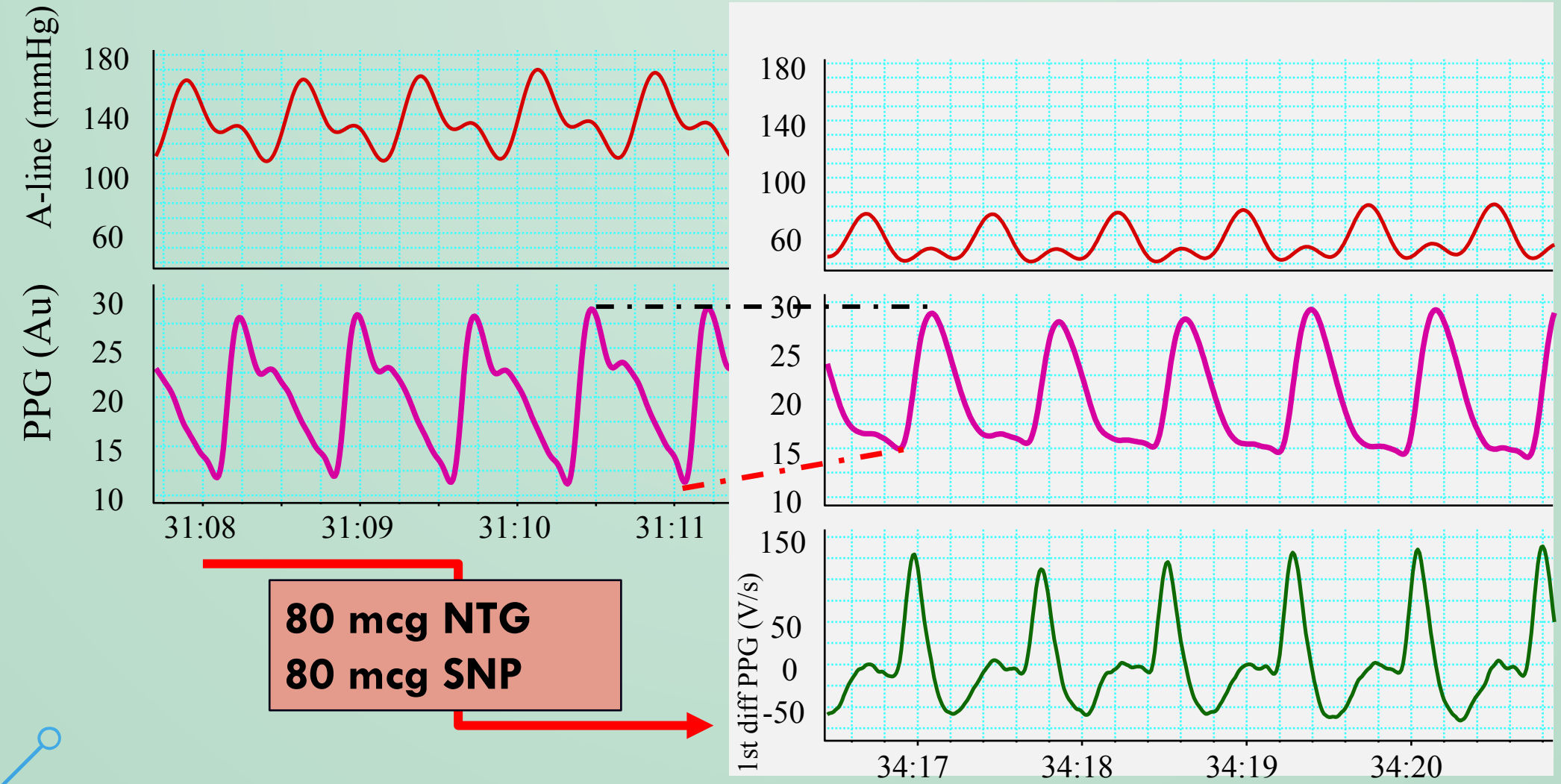
120 mcg NTG
80 mcg SNP

BP = 100/60
PPG AI = 23%



Surgical stimulation
Bp =166/109
AI = 69%
SI=1.65/0.200 = 8.25 m/s

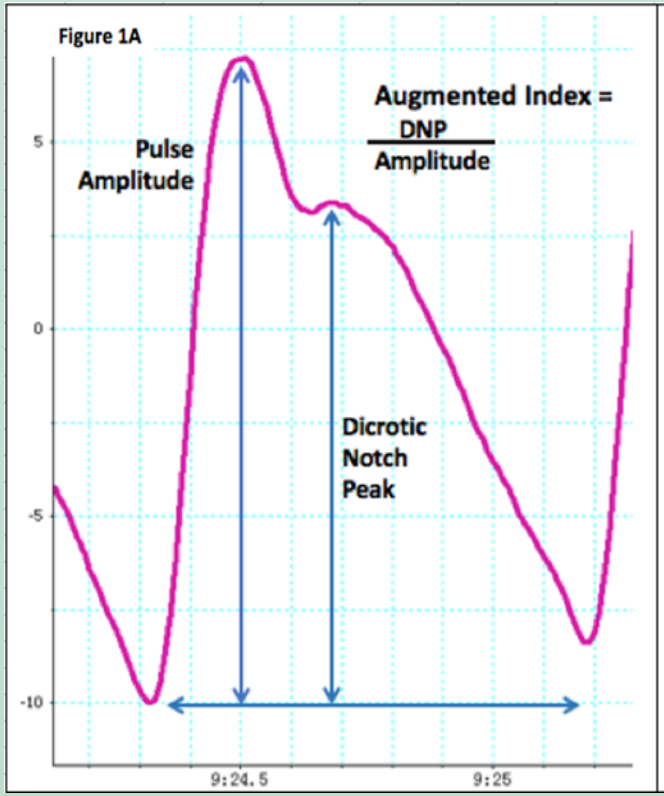
s/p 80 mcg NTG and 80 mcg SNP
Bp =76/42
AI = 5%
SI=1.65/0.418 = 3.95 m/s

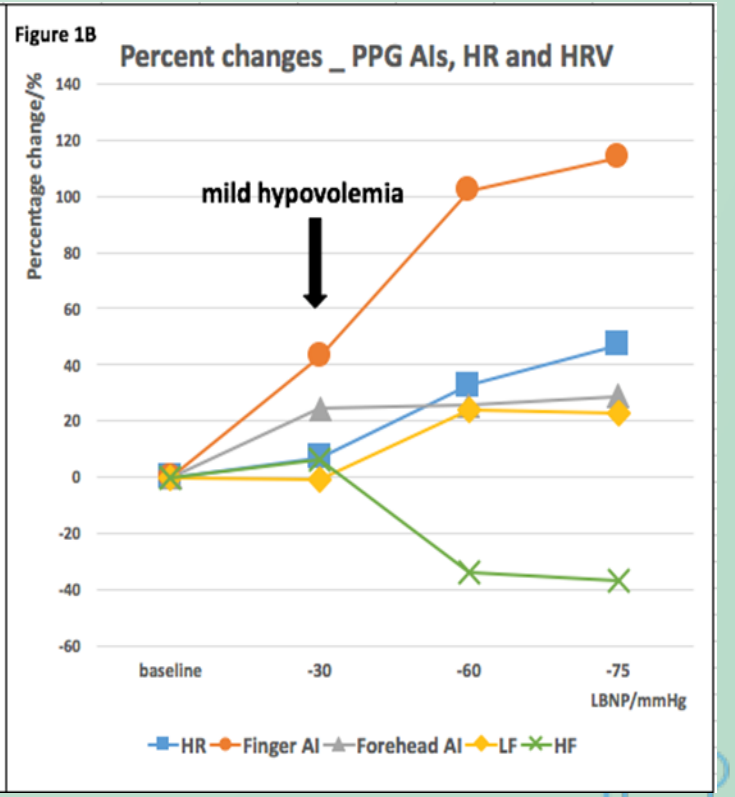


REFLECTIVE INDEX DURING HYPOVOLEMIA

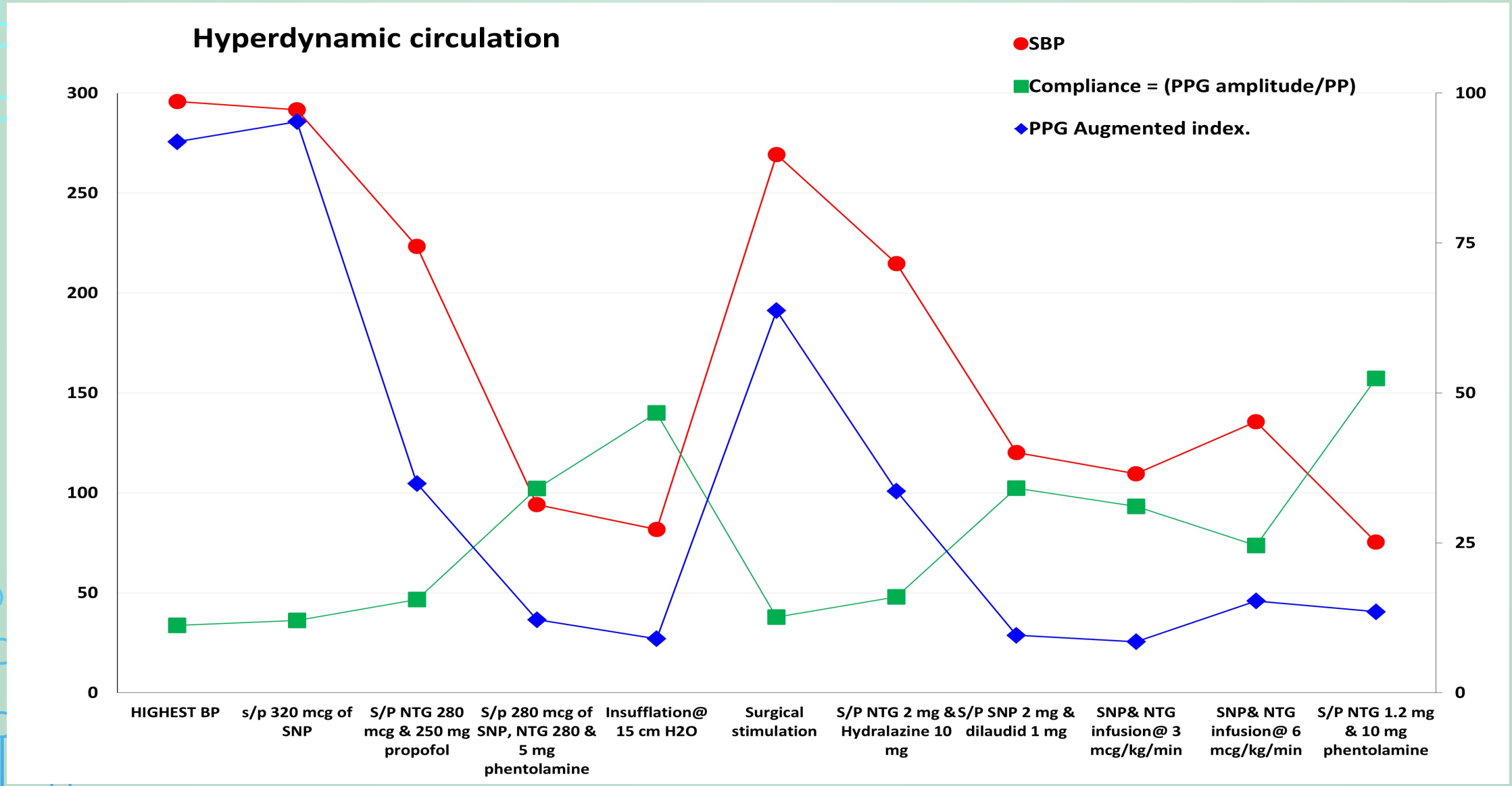
- 17 healthy underwent LBNP protocol 5 min @30, 60 and 75mmHg. At 30 mmHg (≈ 600mL of blood loss ≈ 10% of blood volume),
- HR, HRV and PPG finger & forehead,
- Comparisons were made between baseline and mild hypovolemia (LBNP-30) utilizing Wilcoxon and
- data was expressed as median (1st quartile to 3rd quartile). P value <0.008 was considered significant
- **Conclusion:** Thus PPG AI might be a useful tool to detect mild to moderate hypovolemia.

At mild hypovolemia; the % change of Finger AI was 43%, while the HR was 7%





AI (r value) with SBP=0.93, Local compliance = 0.76



WHO ARE THE PLAYERS?
WHO WILL BUY THIS TECHNOLOGY?

- Fluid management is one of the first line of treatment in hemodynamically unstable patients.
- improvement the fluid management in critically ill patients in crucial. (sepsis, low cardiac output patients). Thus avoiding iatrogic fluid overlaod and worsening outcome
- The closed loop system; when to start/stop giving fluid and when to add vasopressors as second line of treatment.

- **STEP 3: Pathway to FDA approval**

- The pathway to approval for medical device depends on its **risk classification;**

  - **Class 1: General Controls:** devices pose low risk to consumers; such devices are subjected to "**general control**" which ensure the safety and efficacy of the device.

    - **General controls** include; good manufacturing practices, standards and reporting of adverse events to FDA, registration and general record keeping requirements.

  - **Class 2: General Controls with Special Controls**; devices pose more risk to consumers than do class 1, these devices are subjected to "**special controls**" in addition to general controls.

    - **Special controls** include; labelling requirements; device specific mandatory performance standards and device specific testing requirements, post market surveillance, patient registries.

  - **Class 3: General Controls and Premarket Approval (PMA)**; life support devices, such as pacemaker, defibrillators, ventilators. These devices require Premarket approval.

➢ Device pathways to Market:

- **Class 1:** most **exempted** from premarket submission
- **Class 2: Premarket notification [510(k)]**
  - Requires proof that the devices is substantially equivalent (SE) to a legally marketed device that is not subject to Premarket Approval (PMA)
  - The device is considered SE if it has the same intended use and technological characteristics as legally marketed device.
  - If the device is SE to an approved medical device, it is placed in the same class,
  - if it is not substantially equivalent to an approved medical device, it becomes non-SE and is placed into class 3

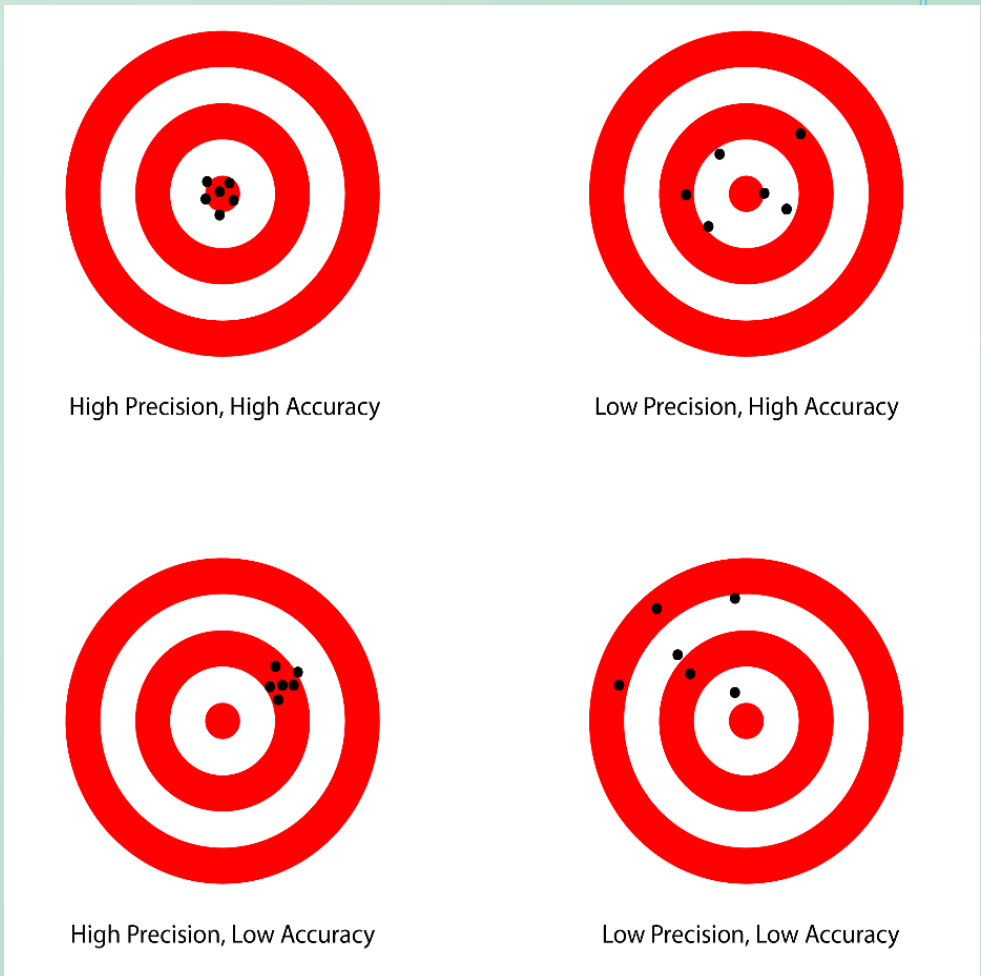
- **Class 3: premarket Application (PMA)**
  - It is a process to reasonably determine that a device is safe & effective (independence)
  - Independence: each PMA should establish the safety and effectiveness of the device under review and that data about one device can't be used to support another
  - The PMA should demonstrate that:
    - the benefits of use the device outweigh the potential risk &
    - The device will be useful for large portion of population

PROOF FOR THE FDA?
HOW TO GO FROM THESE PHYSIOLOGIC OBSERVATION TO A DEVICE ?

- More studies in different population
  - hypovolemic
  - septic
  - CHF
  - vasoactive drugs
- Gold standard issue. (lacking?)
- Precise vs. accuracy
- Safety

REQUIREMENT OF THIS OBSERVATION TO BE

- **Accuracy** refers to the degree of conformity and correctness of something when compared to a true or absolute value
- **Precision** refers to a state of strict exactness, is a measure of the reliability and consistency.
- Something can be accurate on occasion as a fluke. For something to be consistently and reliably accurate, it must also be precise.
- Results can be precise without being accurate. Alternatively, results can be precise & accurate.



- **STEP 1: Device discovery and concept**
- **STEP 2: Preclinical research prototype device**
- **STEP 3: Pathway to FDA approval**
- **STEP 4: FDA Review**

- If medical device developers have enough information on device's safety and effectiveness, they can file an application to market the device to the public.
- **Premarket notification or [510(k)] for class 1,2 devices**
  - Indicates that the Class 2 device is similar to others legally marketed devices.
- **Premarket Approval Application (PMA) for class 3 devices**
  - It includes all nonclinical and clinical studies
  - FDA will check for good manufacturing practices (inspect the manufacturing lab and facilities)
  - FDA Advisory committees (groups of experts who provide the FDA with their independent advice a bout the product)

Step 5: FDA Post-Market Safety Monitoring

- FDA continues to monitor device performance and safety after the device has been approved
- Manufacturing inspections
  - (routine visits to the facilities to check the adherence to good manufacturing practices)
- Reporting Problems
  - (MedWatch), FDA adverse event reporting program for drugs & devices.
  - Medical Product Safety Network (MedSun), an adverse events reporting program
- Active surveillance
  - to keep an eye on approved medical products in real time (using electronic heath data bases ,e.g. electronic health records systems)

LIMITATIONS

- pulse oximeter is noninvasive, readily available first line monitor, that is robust, safe, accurate, reliable, and easy to operate and requires no calibration.
- However, clinicians must be aware about the limitations of this technology and the common drawbacks of most noninvasive measurements.
- patient-related factors (such as local temperature and blood flow)
- specific technical capabilities (such as time response, noises, margin of error, etc).
- Furthermore, the performance of oximeter-dependent calculations will be below the accuracy of standard invasive techniques. (nature of noninvasive monitor) but will constitute a valuable first-line monitoring approach in patients in whom invasive monitoring are not indicated

DESIRABLE CHARACTERISTICS OF NEWER PULSE OXIMETERS

TO ENABLE NEW CLINICAL APPLICATIONS AND/OR IMPROVE THE STANDARD ONES

- the ability to disable the autogain and autocenter functions
- to eliminate certain signal filtering
- to improve the time resolution (usually between 8-12 sec)
- to show red-infrared data of PPG.
- The access to real and unfiltered raw data

THANK YOU