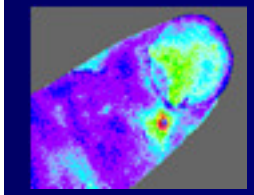
Microvascular Imaging and Clinical Applications



John Allen

Lead Clinical Scientist

Microvascular Services

Northern Medical Physics and Clinical Engineering,
Freeman Hospital.

Reader in Microcirculation, Newcastle University.

“LIGHT”

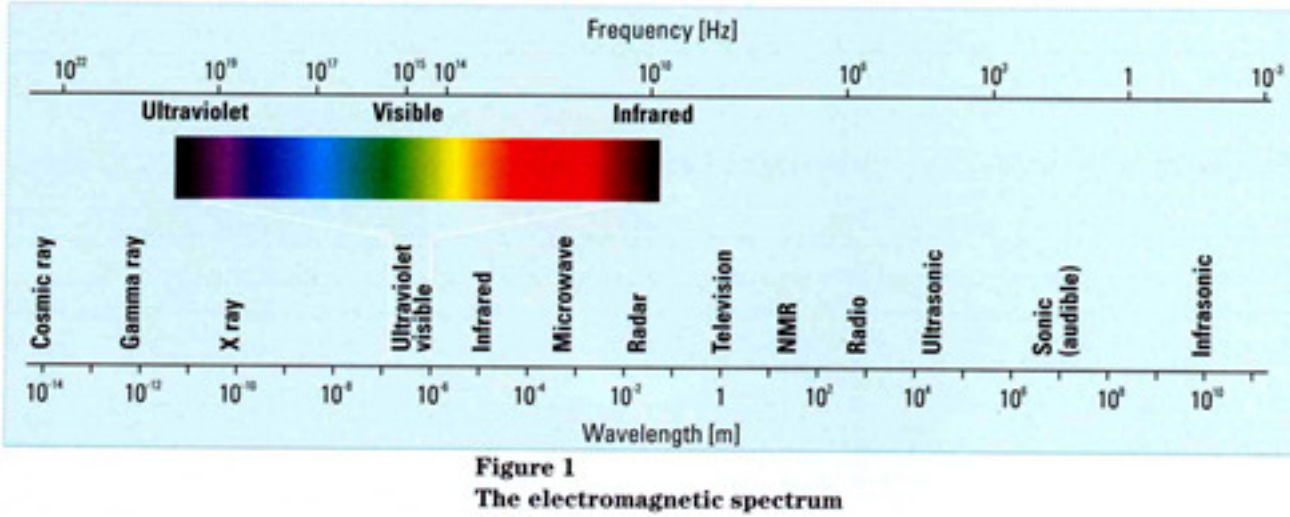
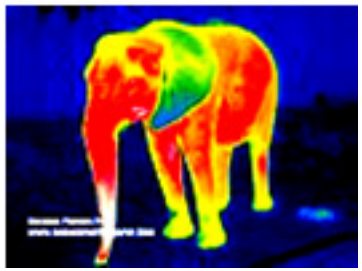


Figure 1
The electromagnetic spectrum

“Focus on optical diagnostics: VIS & IR”



Context: NHS Clinical and R&D

- *Vascular Optics* theme - small blood vessels.
- Significant medicine component.
- Imaging and non-imaging assessments.
- State-of-the-art measurement facility (FH).
- Clinical service : 1000+ annually for North England.
- Collaborative links with industry.
- Device and Novel Measurements R&D: **2014-19 : CI/Co-I ~£1.6M R&D funding in theme (NIHR i4i funding mainly).**

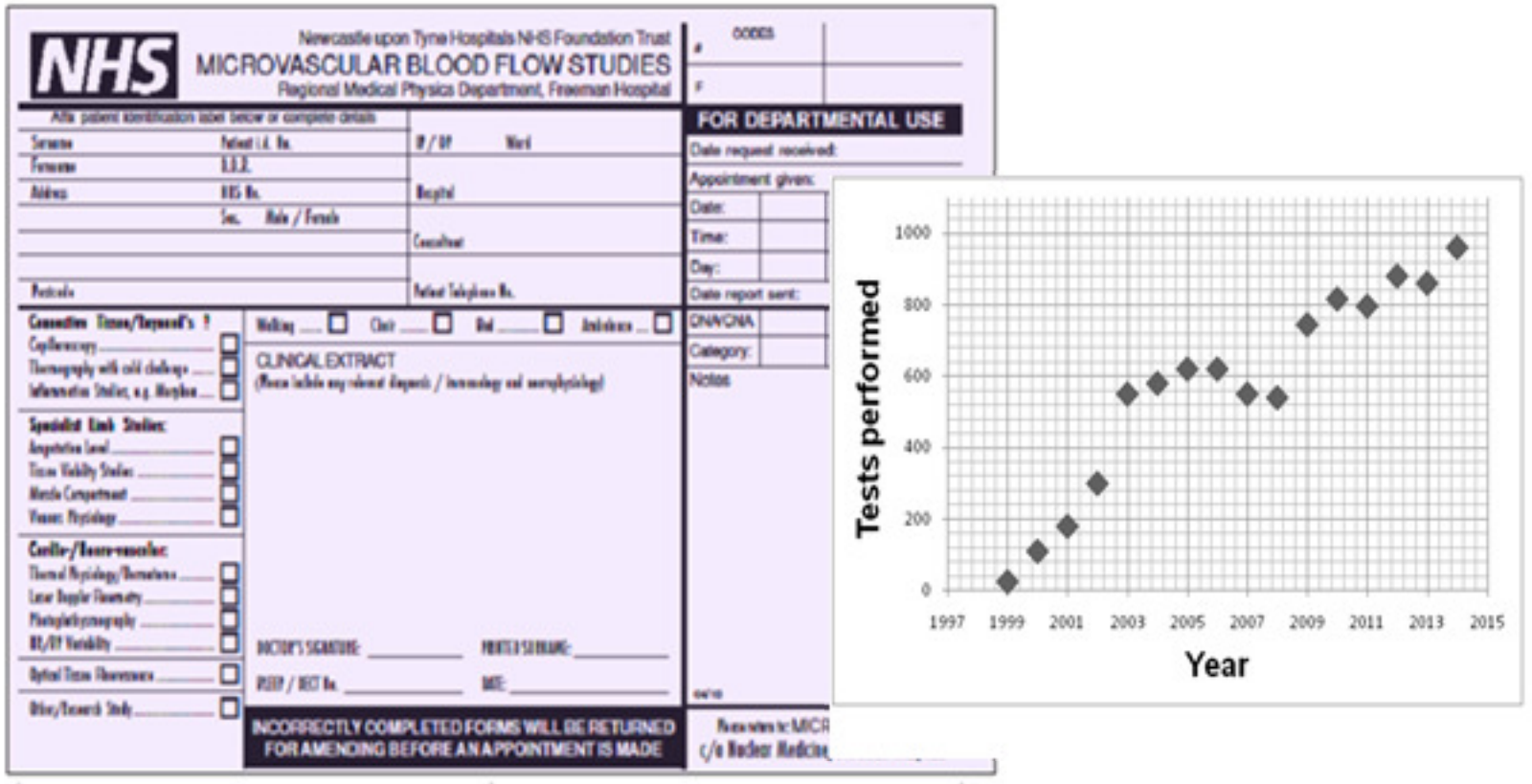
Paper: Microvascular Imaging (MVI): Techniques and opportunities for clinical physiological measurements

John Allen and Kevin Howell

Topical Review paper for: Physiological Measurement. 9 techniques.

= Capillaroscopy, TI, LDI, Speckle, Hyperspectral, iPPG, TVI, SO2, + OCT

Portfolio – “Microvascular”

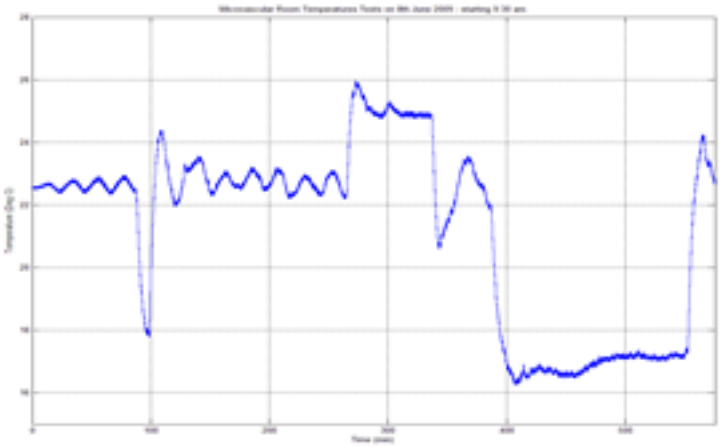


Key application area: Connective Tissue Disease (CTD) / Raynaud’s

We currently use [1] Thermal Imaging and [2] Capillaroscopy for this ...

Clinical Measurement setting (Freeman Hospital)

- Tightly controlled temperature and humidity (23 °C, ~40% RH).
- Minimal circulating draughts.
- Operating range 15 to 32 °C.
- Transition attainable 0.5 °C/min.
- Designed for medical thermography.



Microvascular @ Medical Physics

Audrey Macdonald

Tim Powell

Steve Burnett

Sam Urwin

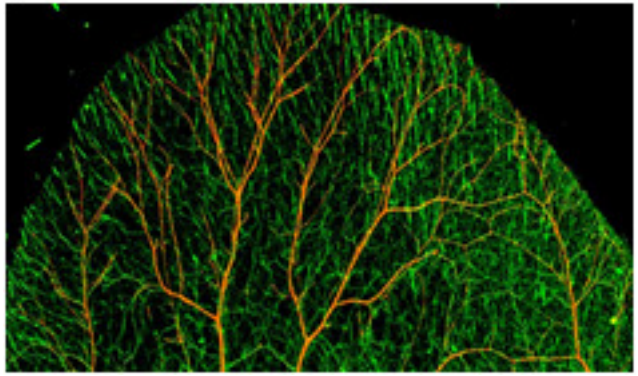
Sadaf Iqbal

Emma Scott

Microvascular service lead – a varied role

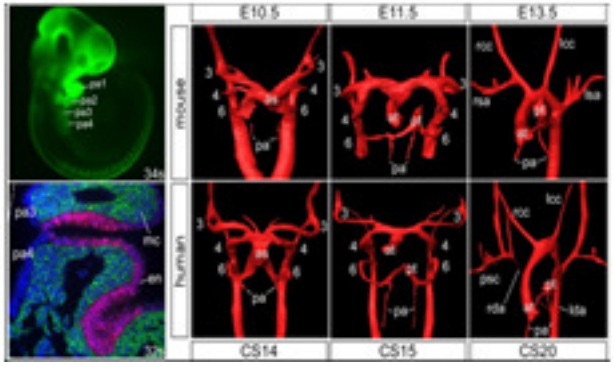
- Patient measurements. Reporting.
- Management. Securing resources.
- Calibration // QA.
- Quality Improvement (QI). Resilience.
- IT.
- Health and Safety.
- Clinical Governance.
- **Service development.**
- **Clinically focused research.**
- All good for our CQC inspection of Trust.

Newcastle University http://www.ncl.ac.uk/cardio/research/vasculardisease/

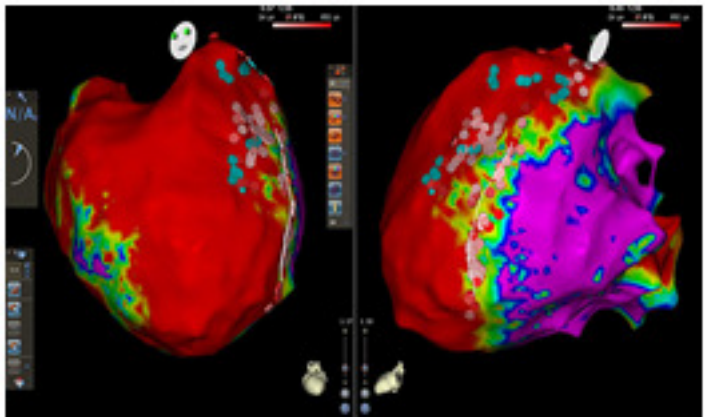


Vascular disease

Congenital heart disease



Myocardial disease



Professional associations:

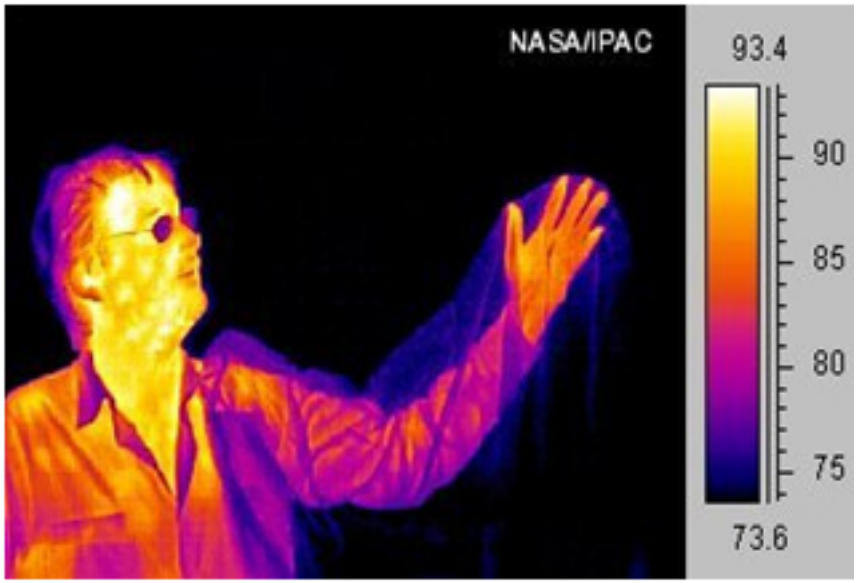
European Association of Thermology (EAT)

http://www.eurothermology.org/

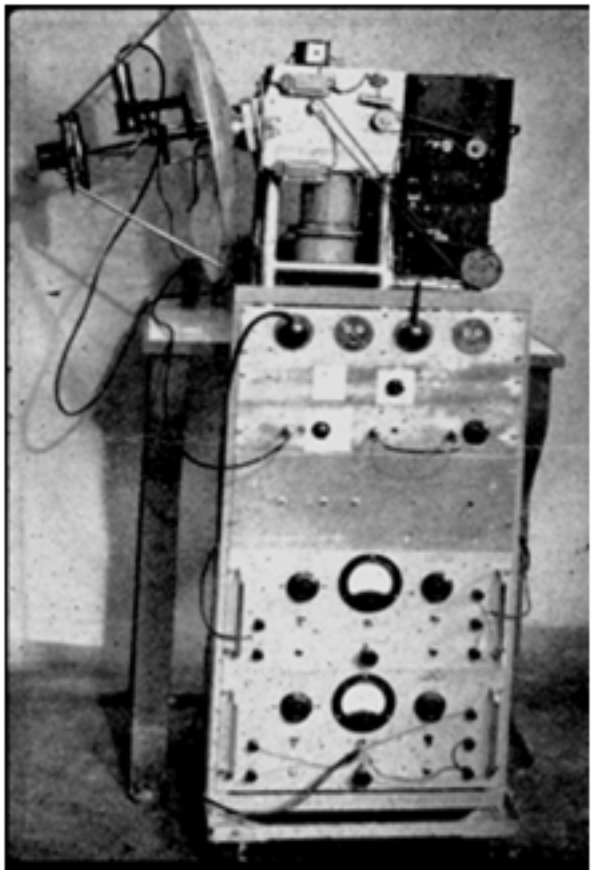
Institute of Physics and Engineering in Medicine (IPEM)

Thermal Imaging (TI)

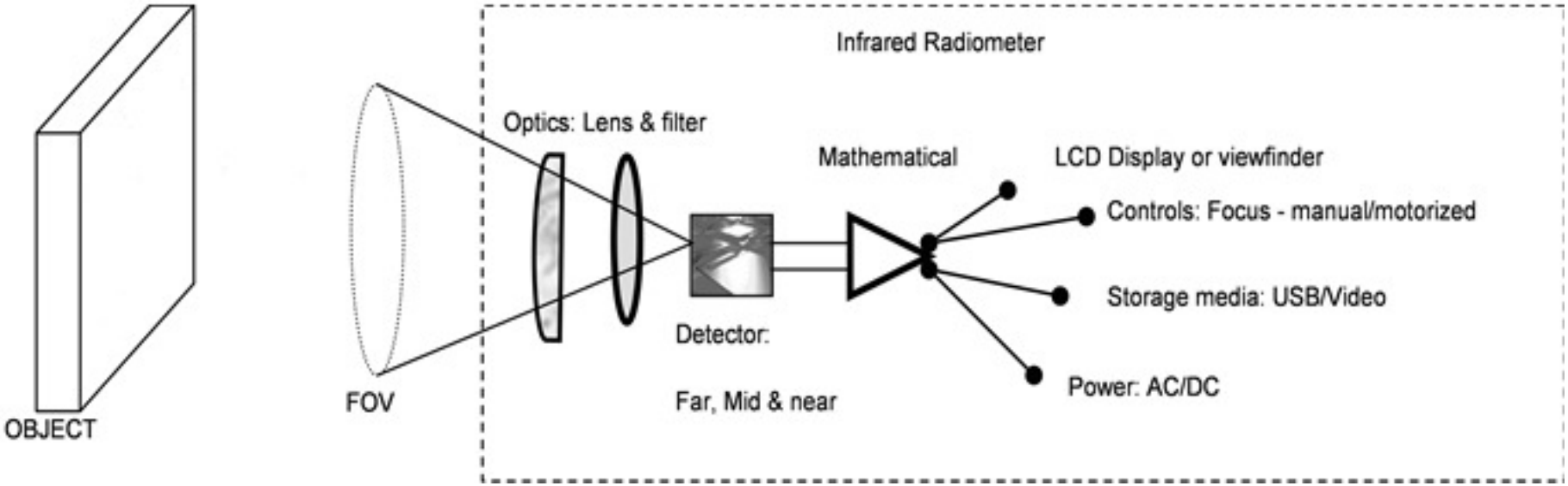
Optical properties of materials can behave in unexpected and potentially useful ways…



Pyroscan prototype - thermogram of arthritic knee Pyroscan 1958



Schematic of a modern thermal imaging system …



Infra Red Radiation

discovered

in 1800

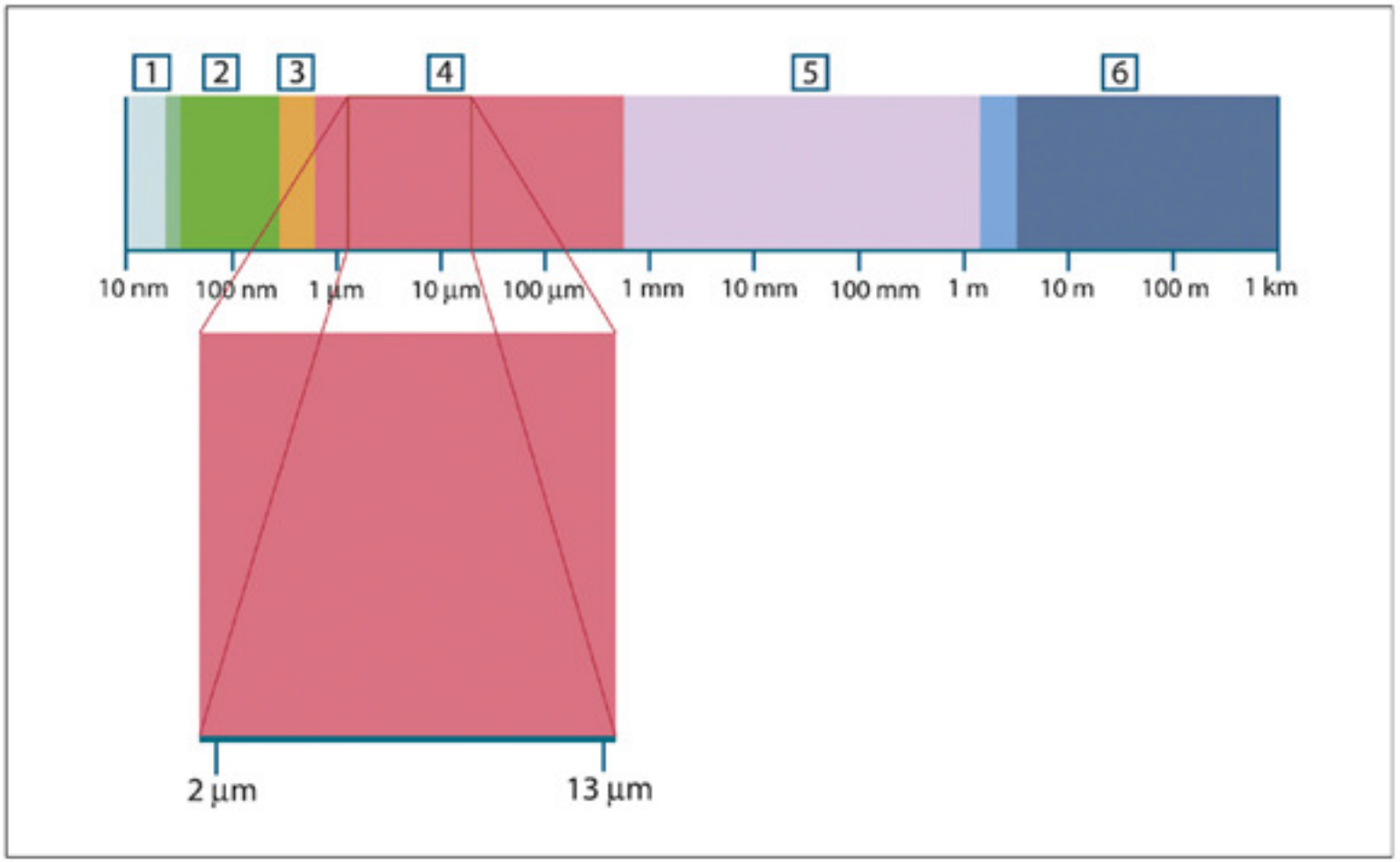
by

Sir William Herschel

Reported in the Philosophical Transactions of

The Royal Society, London

The electromagnetic spectrum



The electromagnetic spectrum. **1:** X-ray; **2:** UV; **3:** Visible; **4:** IR; **5:** Microwaves; **6:** Radiowaves.

Image from: Flir ThermaCAM™ Researcher User's Manual Professional Edition v2.8

How do we know how much radiation is being emitted? - Some formulae

Planck's law

Emittance, $W_{\lambda b} = \frac{2\pi hc^2}{\lambda^5\left(e^{hc/\lambda kT} - 1\right)} \times 10^{-6}[Watt/m^2, \mu m]$

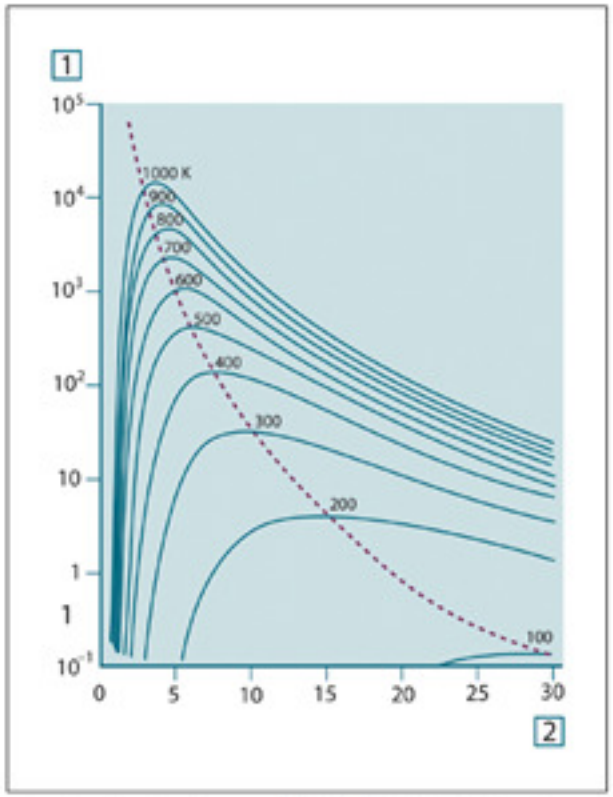
Wien's displacement law

$$\lambda_{max} = \frac{2898}{T}[\mu m]$$

Stefan-Boltzmann's law

$$W_b = \sigma T^4 \ [\mathrm{Watt/m^2}]$$

Area under the curve



1: Spectral radiant emittance (W/cm² (µm)); **2:** Wavelength (µm).

Eg. Each person radiates about 1kW

Image from: Flir ThermaCAM™ Researcher User's Manual Professional Edition v2.8

All objects at a temperature above absolute zero emit energy (*Stefan-Boltzmann Law*).

Detected power calculated from:

$$Q \propto \sigma \varepsilon A T_{abs}^{4}$$

σ is Stefan-Boltzmann constant ($5.67 \times 10^{-8} Wm^{-2}K^{-4}$),

A is the surface area of the object,

ε is the **emissivity** of the material (**skin ~1**). [we use 0.98]

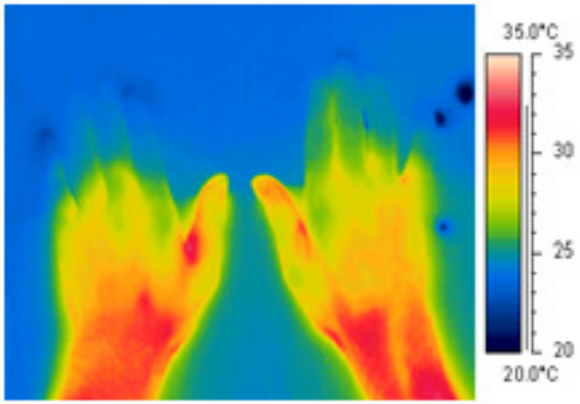
Above calculates power detected over all wavelengths - needs adapting for a thermal imager / optics sensitive to IR across quite just a narrow bandwidth:

$$Signal = \varepsilon f(T_{abs})$$

Medical thermal imaging

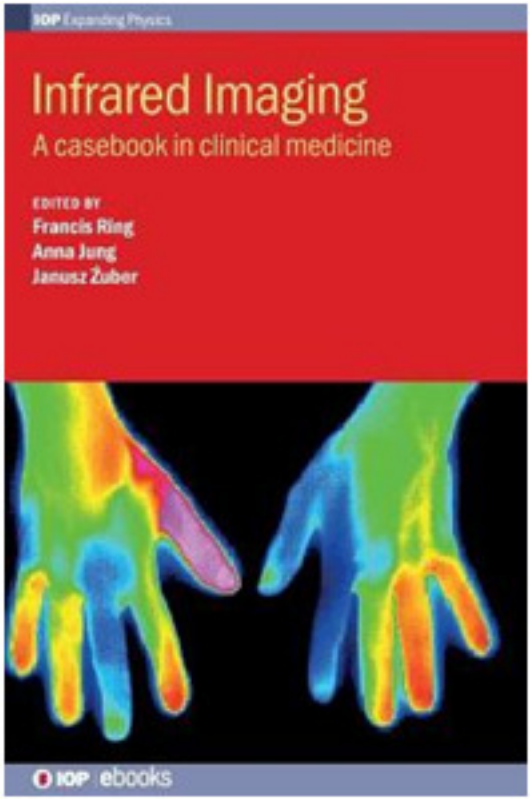
FLIR
A655sc
camera

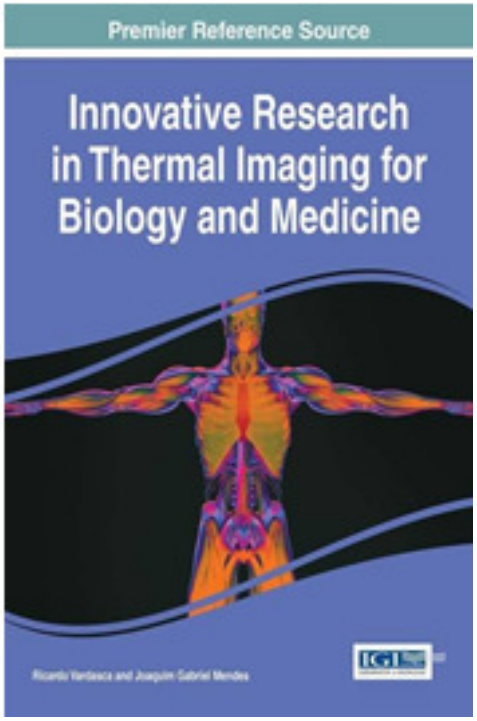
FLIR
Lepton:



Land P80P thermal black body reference

Evidence base / Guidelines ?

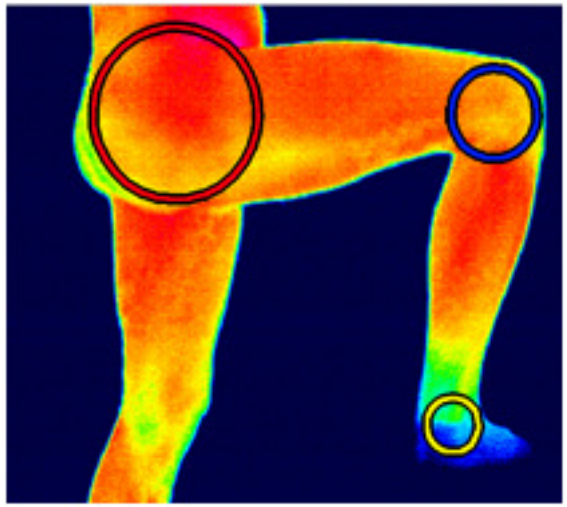
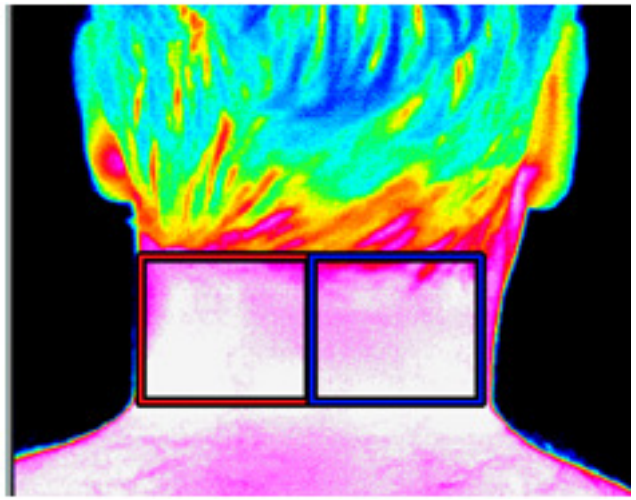
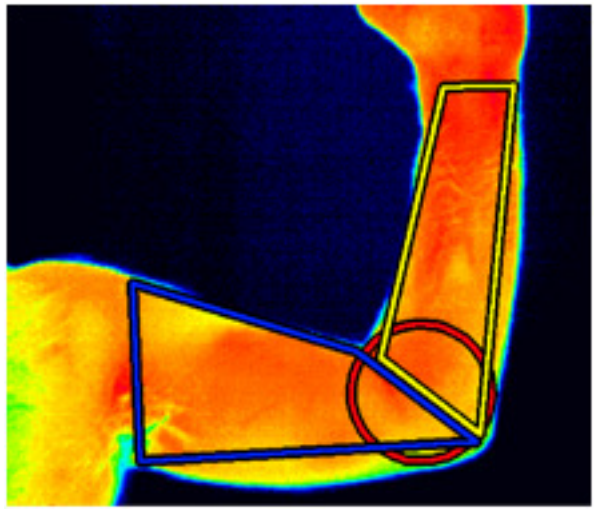




Standard poses and regions of interest

- K. Ammer, B. Jones & Medical Computing Group @ University of South Wales

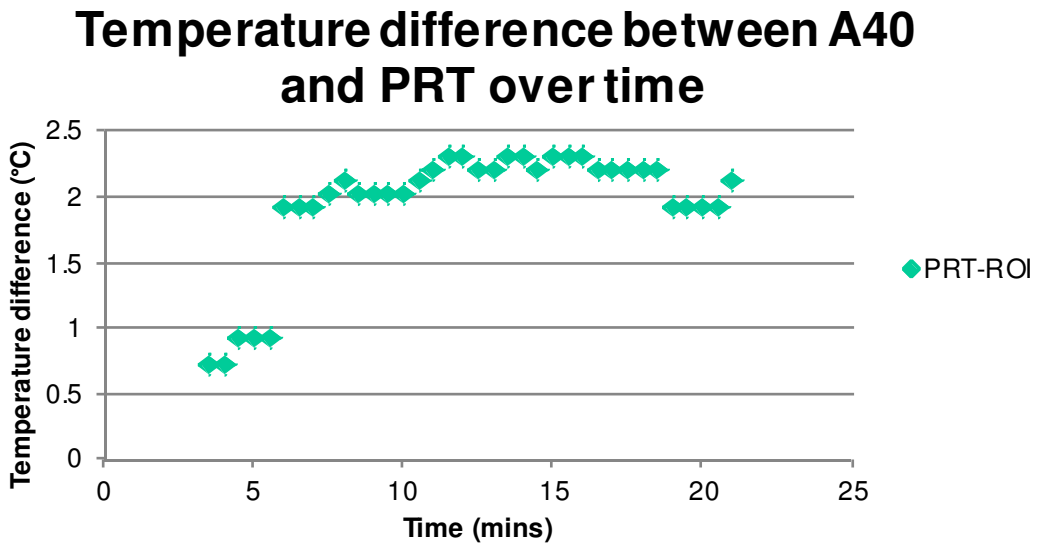
- 24 standard views of human body
- 87 regions of interest

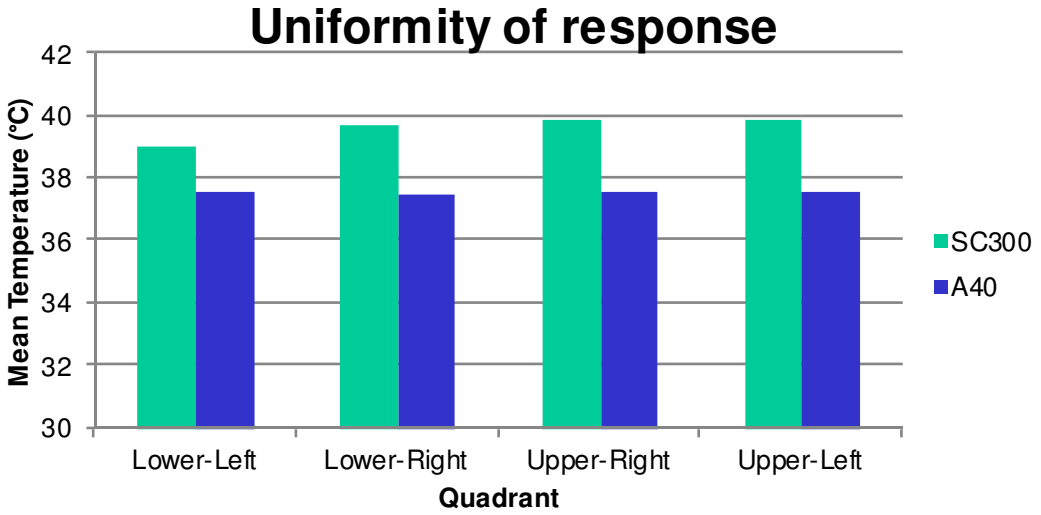




Need reliable imaging

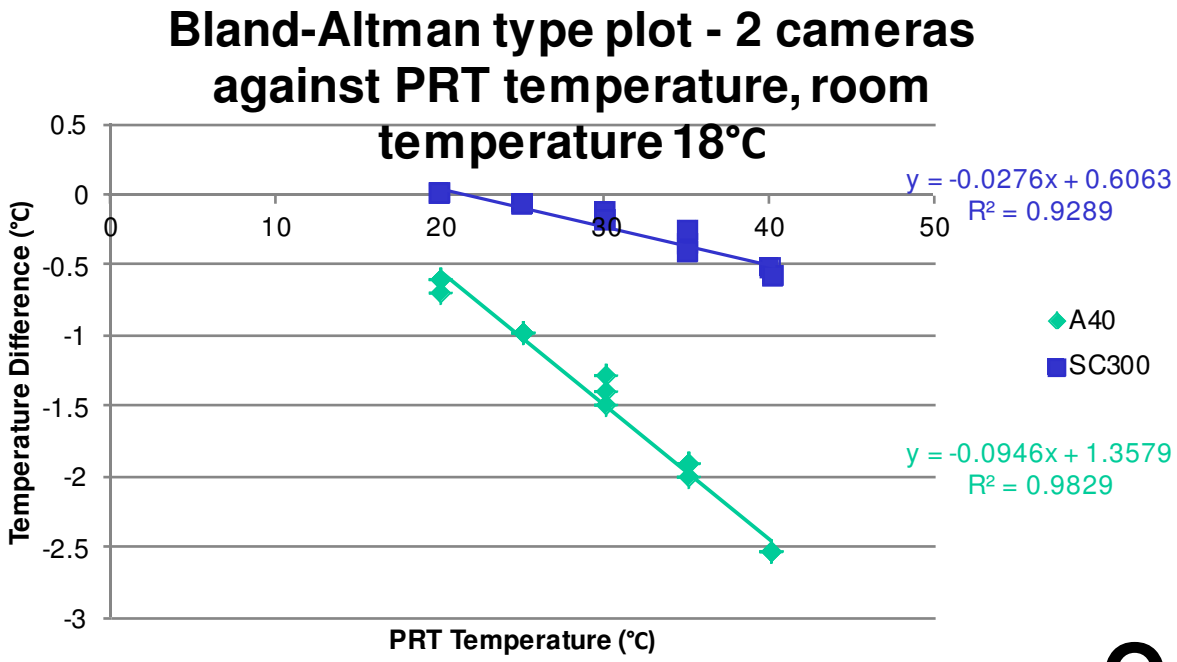
Need to know characteristics of thermal imager

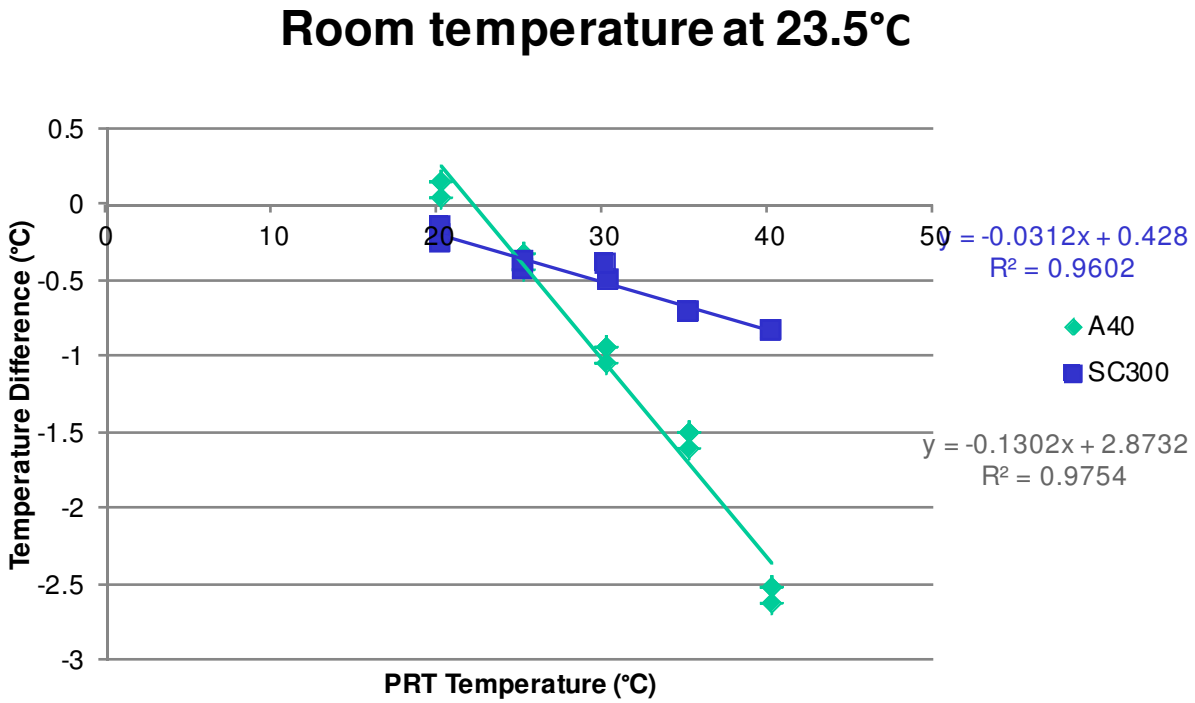
QA Camera tests 1



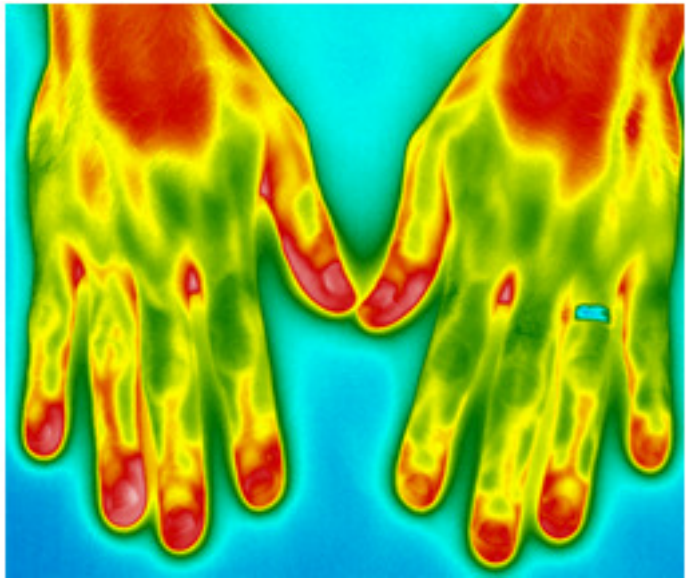


QA Camera tests 2





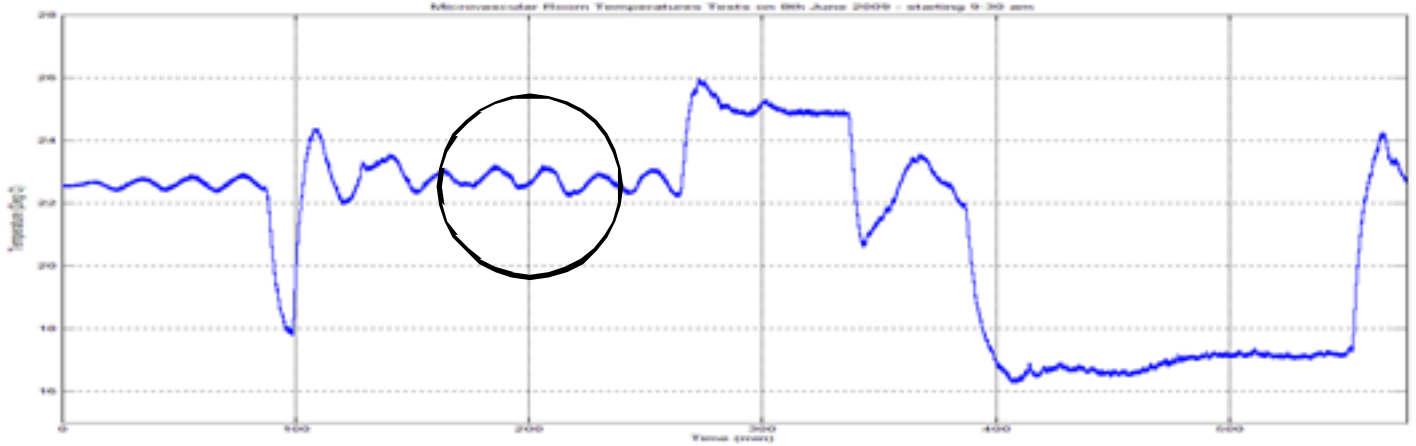
MV Imaging system being replaced



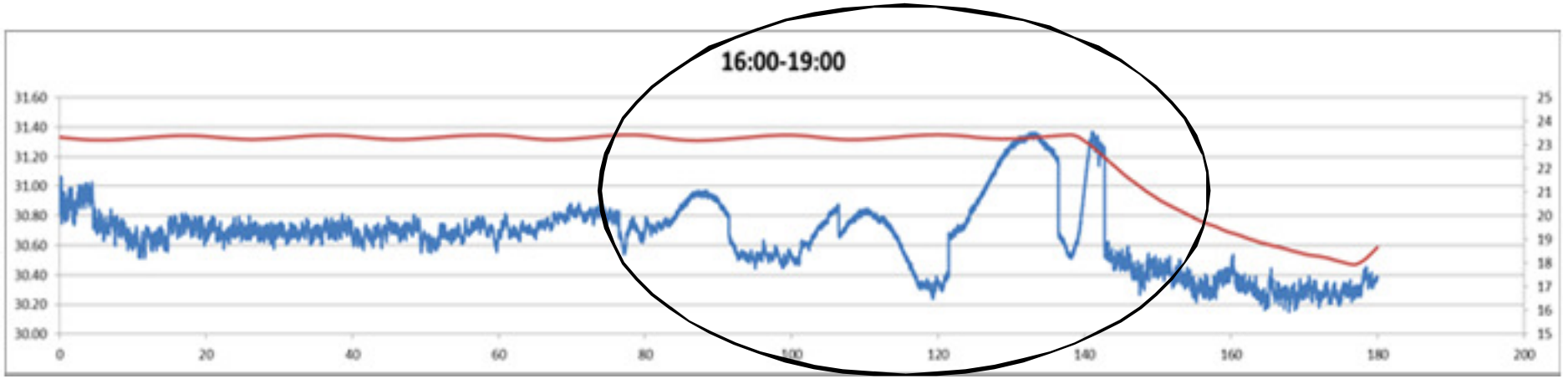
FLIR A655sc camera
640 x 480 pixels

It is essential to have QA procedures …

Calibration / QA / testing vital!



It is essential to have QA procedures … Our new FLIR A655sc camera



Fundamentals: de-risking

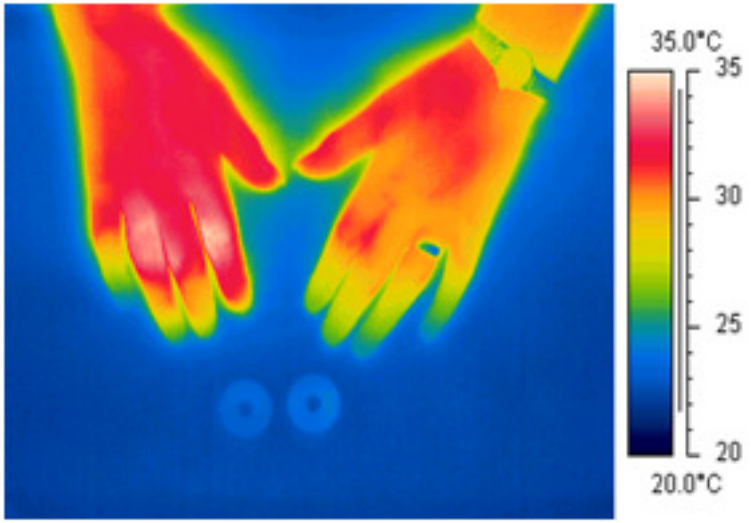
Training in measurements + reporting

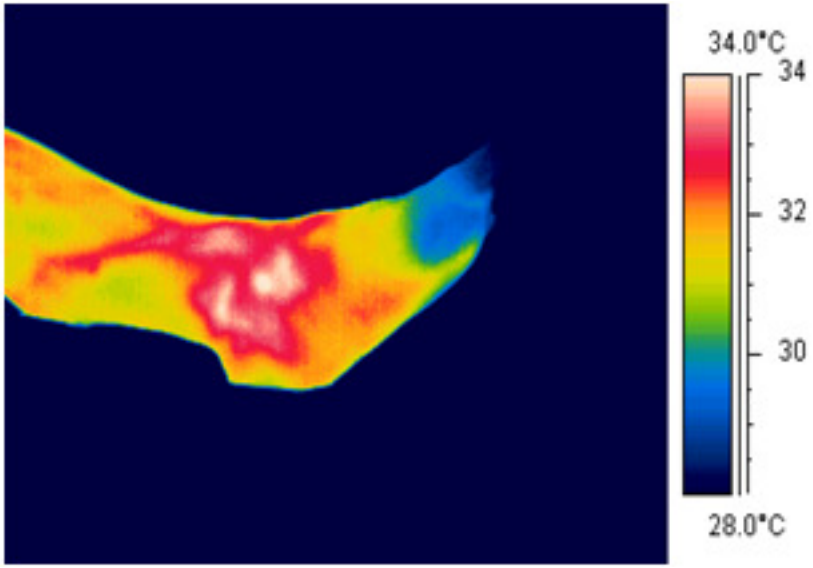
Risk Assessment

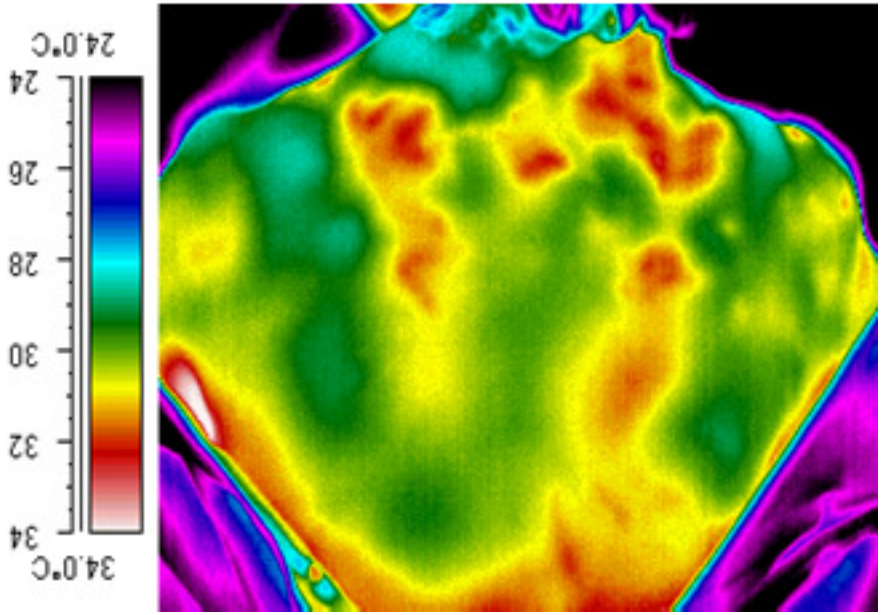
Quality Assurance / Calibration

External audit

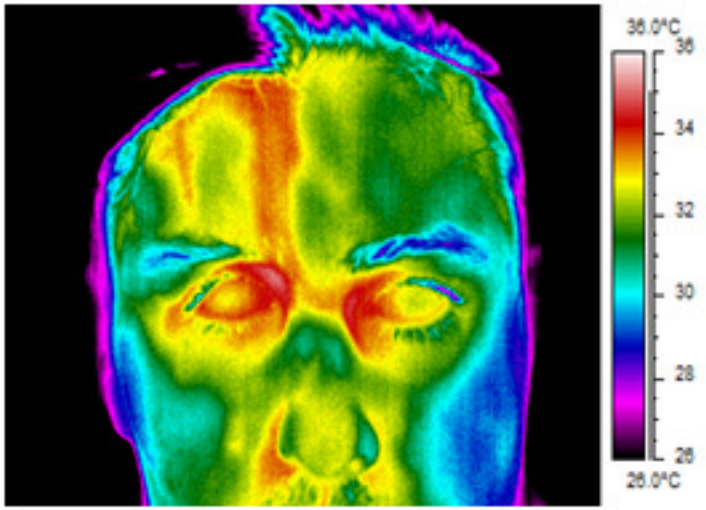
Inflammation assessments

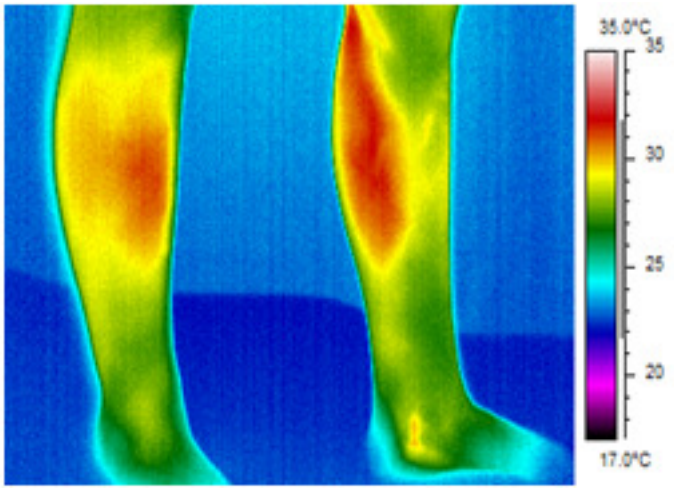


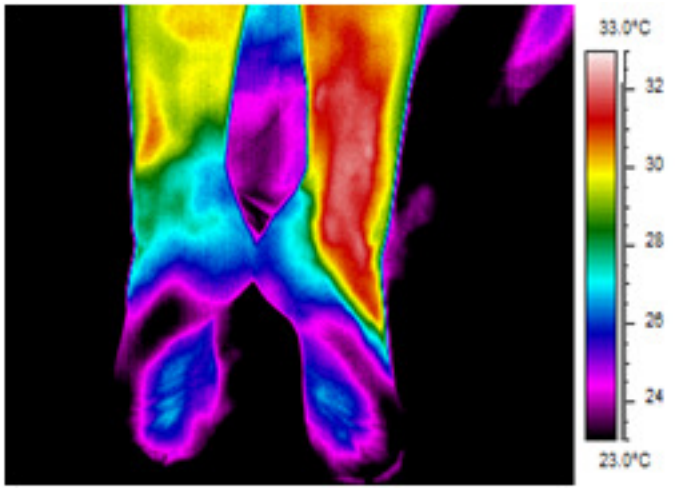


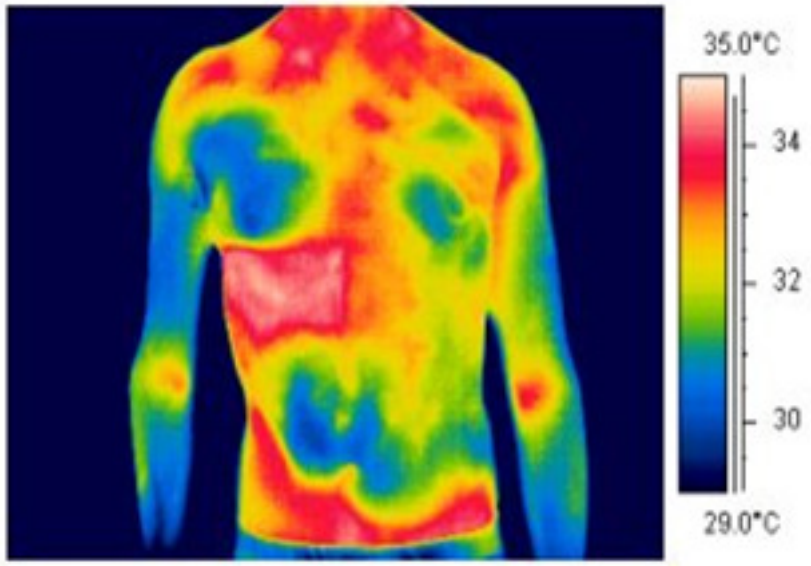


Example “morphea” scans

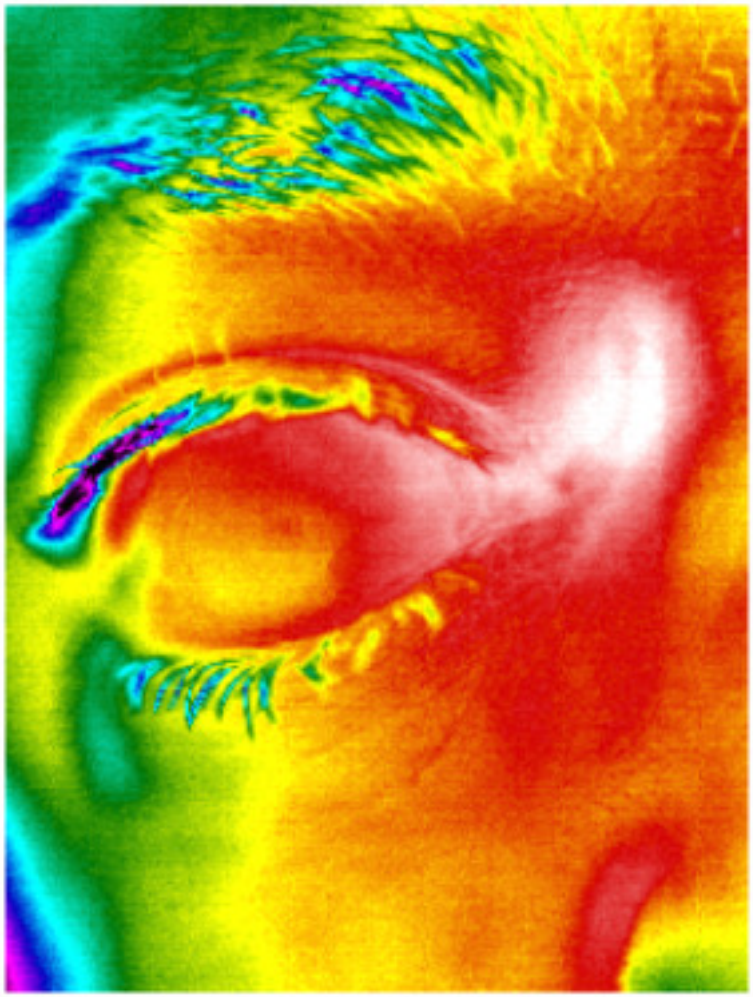






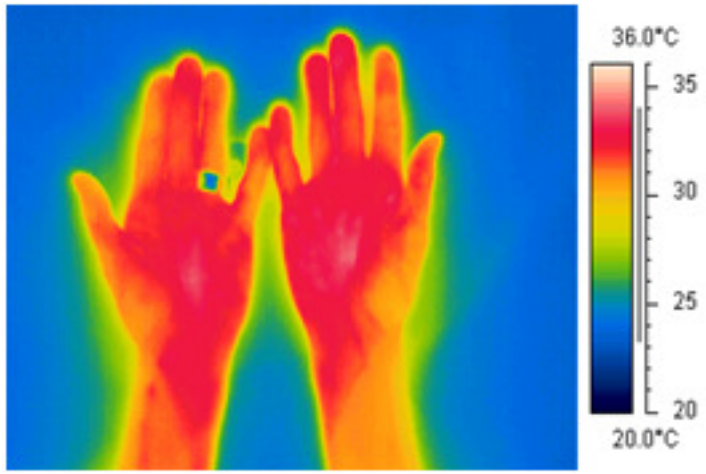


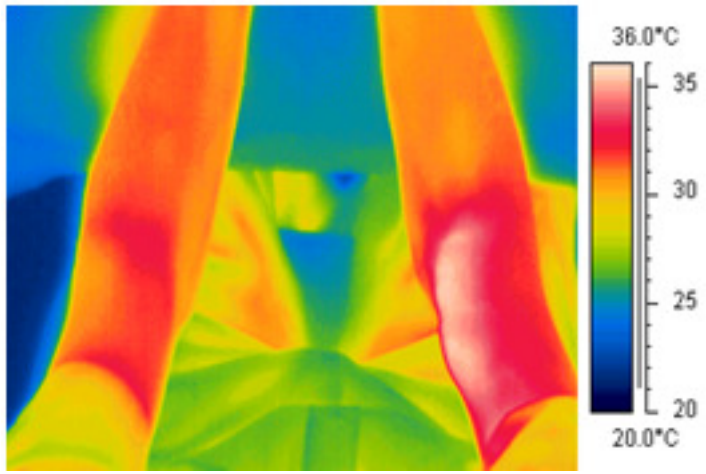
Knowing the indirect symptom(s) of a disease …



= Thyroid [eye] disease

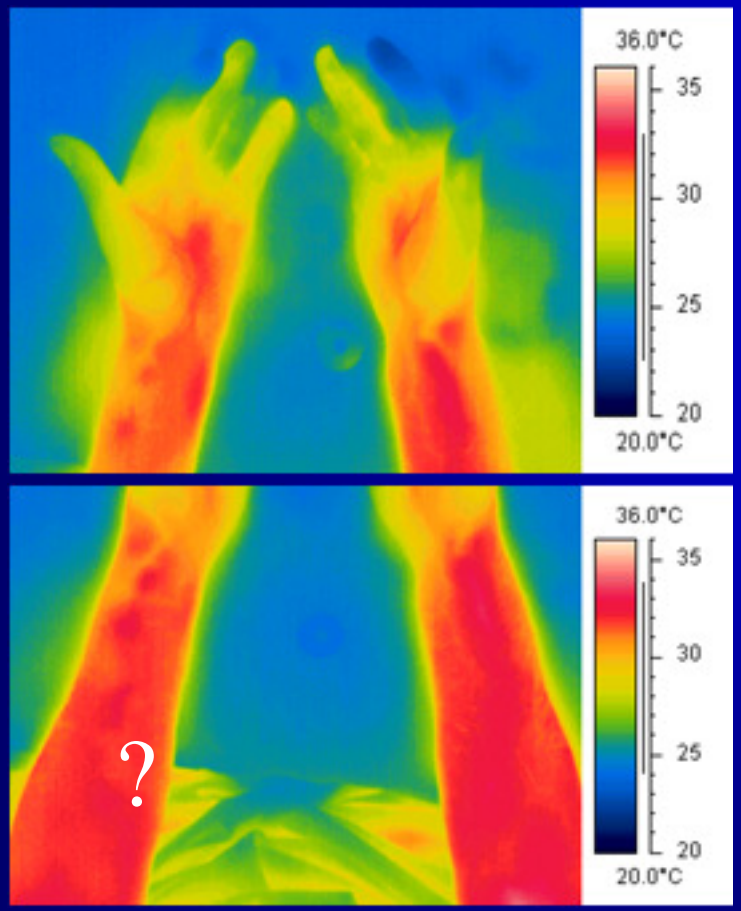
Renal Fistula assessment



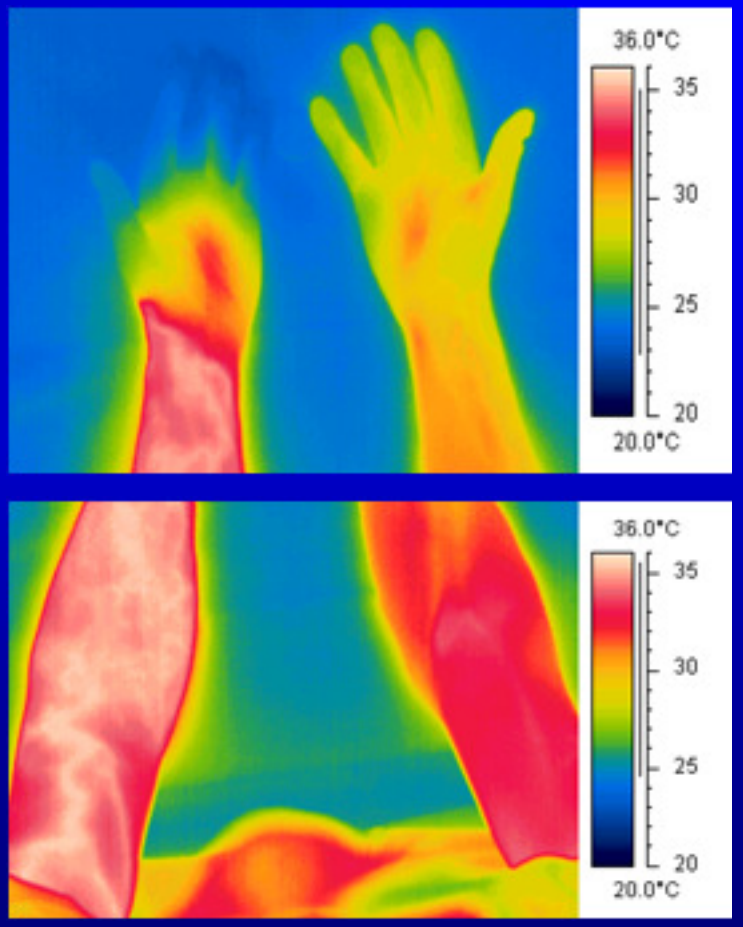


Brachial fistula

Examples : Problem fistulas

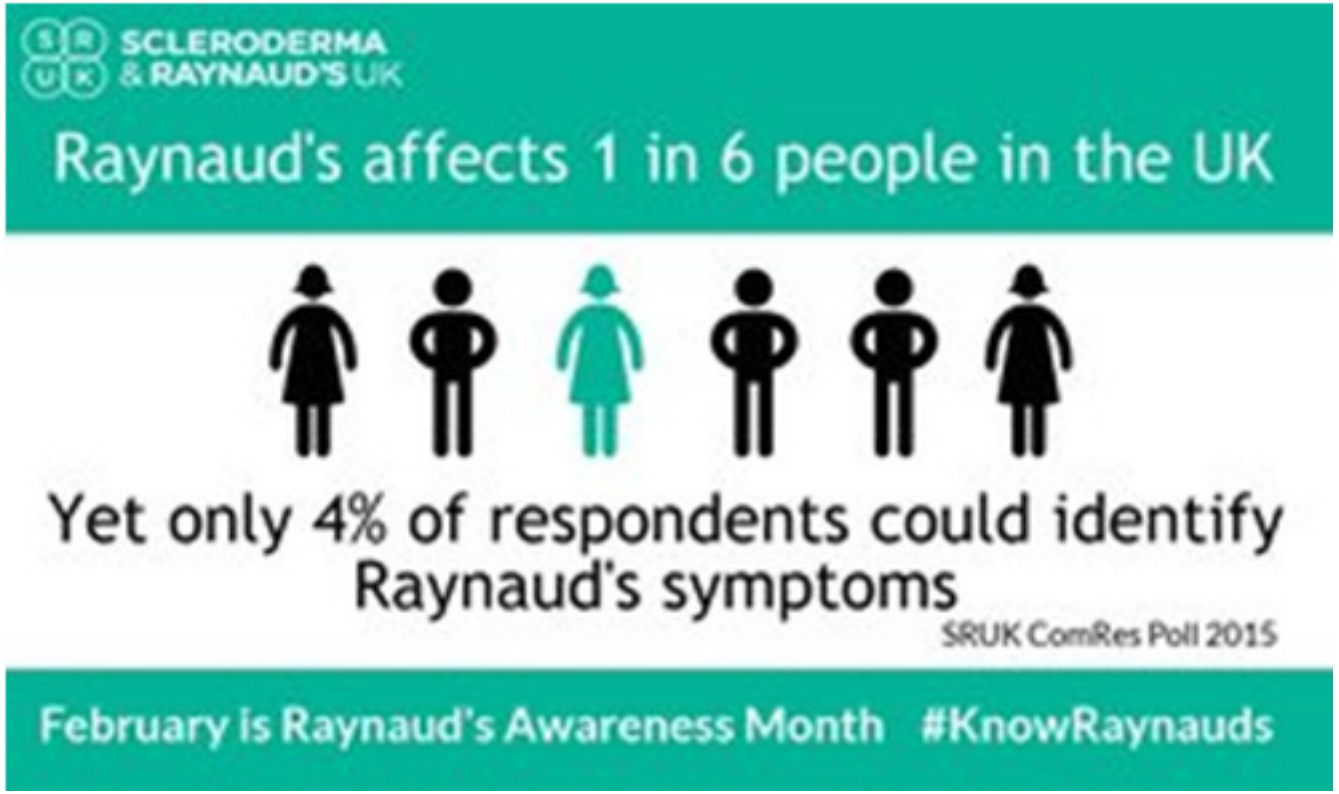


Patient 1 (Radial)



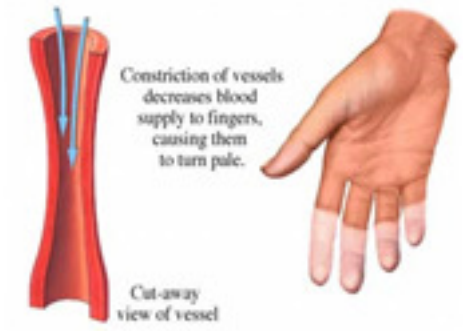
Patient 2 (Brachial)

Raynaud's Phenomenon (RP)



Raynaud's phenomenon (RP)

WHITE **BLUE** **RED**



?Evidence for Primary or Secondary Raynaud's

Systemic Sclerosis (SSc)

- Varied presentation:
- Fibrosis of skin & internal organs
- Thickening, hardening and tightening of skin
- Extent of skin involvement allows classification

- **<u>Usually Raynaud's</u>**…

Examples of abnormal thermograms (secondary Raynaud's – CTD)

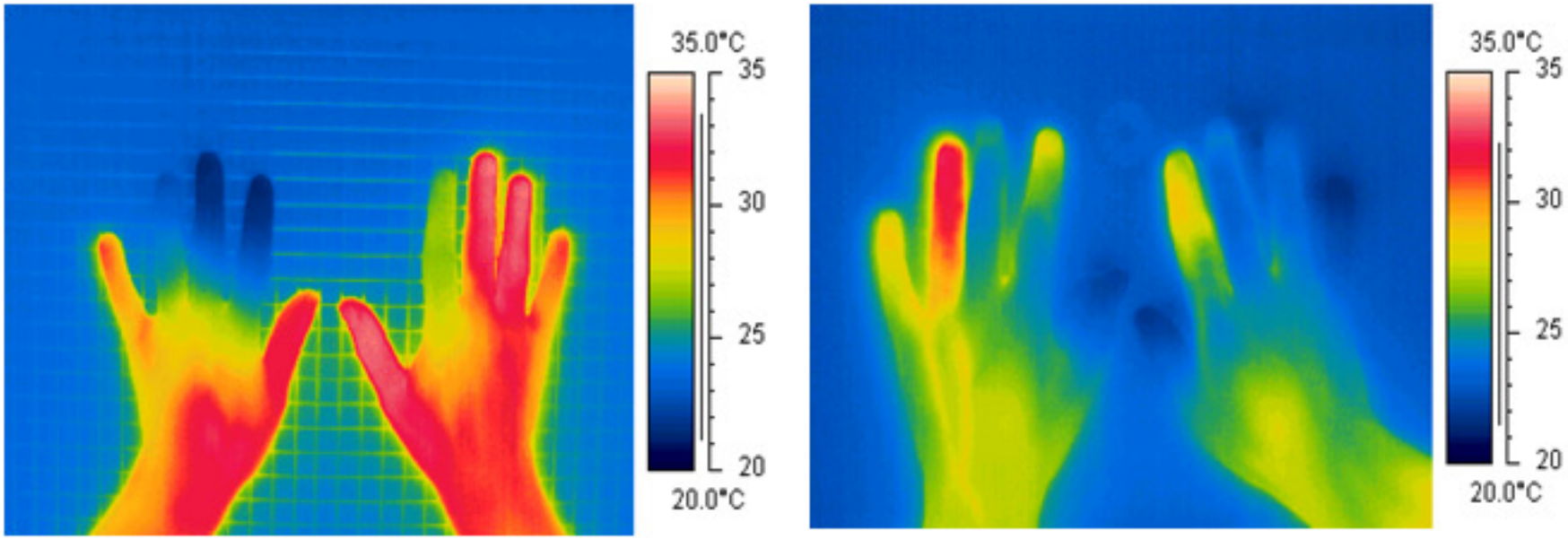


Image interpretation needs medical history / knowledge of neurophysiology and immunology

Cold challenge provocation …

- Temperature response to mild cold challenge
- Assess degree of vasospasm in the peripheral circulation to cold
- Post-challenge expect healthy subjects to have rapid symmetrical re-warming of finger tips. Fingers of Raynaud's patients greatly delayed …

- Measurement protocol important.

Pre-test protocol notes:

Don’t run a marathon.

Don’t smoke 20 cigs.
Don’t drink a gallon of coffee cola / tea.

Avoid snow ball fights.

Wear sensible clothing on way to testing.

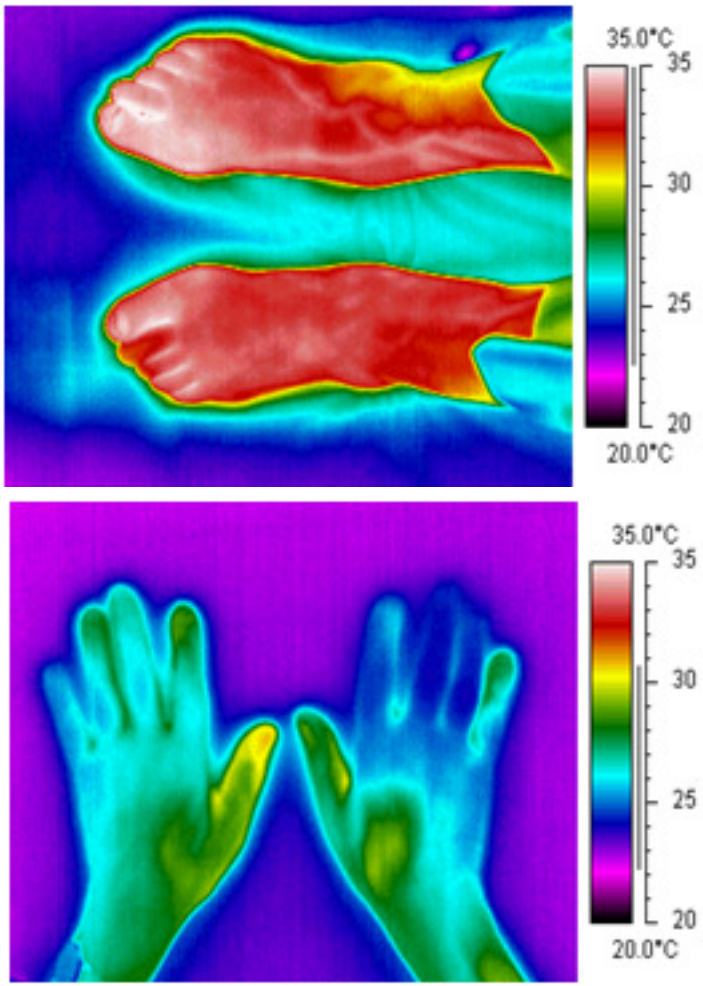
Don’t use skin creams / talc on target measurement sites.

%

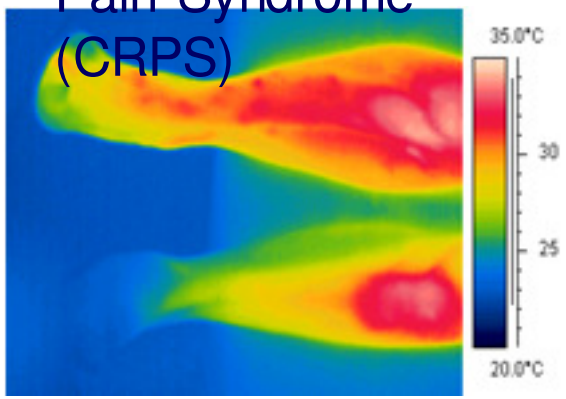
Arrive in good time for test. Patients to acclimatize at least 30 mins before imaging commences.

Feet?

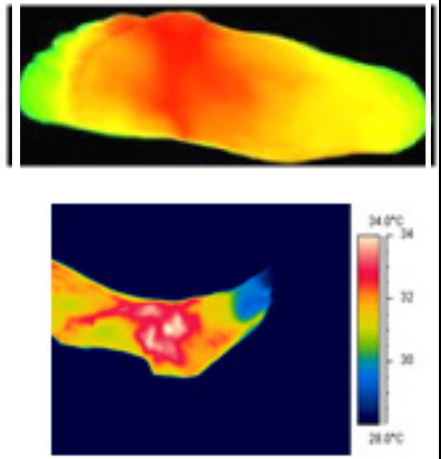
Erythromelalgia



Complex Regional Pain Syndrome (CRPS)



Diabetes



Non freezing cold injury (NFCI)

TI cannot be used blindly…

What is this?

Some challenges / mitigation:

* Camera can be poor for absolute temperature readings.
* Camera properties can change with ambient temperature.

* TI is sensitive to possible abnormalities but not specific to a disease. Dual+ pathologies?

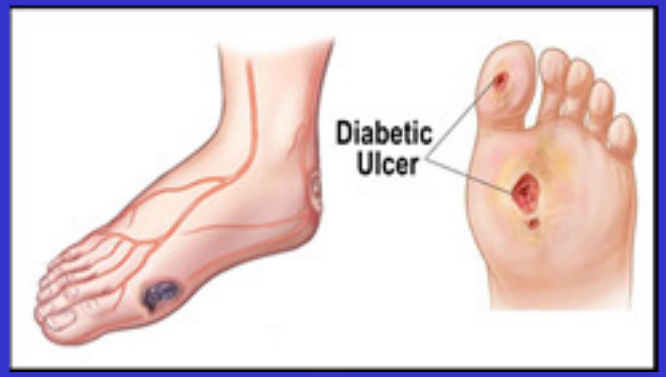
*Claims made about diagnostic abilities of a camera. Thermography produces nice images – expectations high!

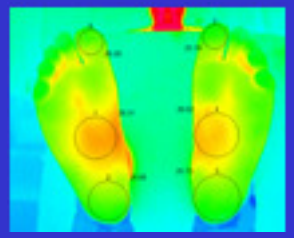
* Poor pre-test protocol use / compliance.
* Lack of training / opportunities in medical thermography.
* Lack of standardization.
* Reporting of images by those not involved in the test.

*Evidence base – beware of the Case Study. Normal ranges?

Device development - Innovative diabetic foot ulcer prediction

UK Consortium : ~£1.2M Awarded
NPL industry led project. UKCRN Portfolio



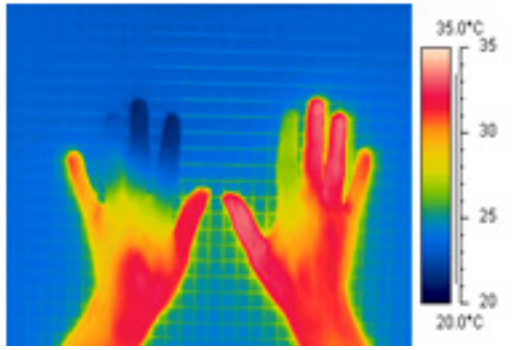


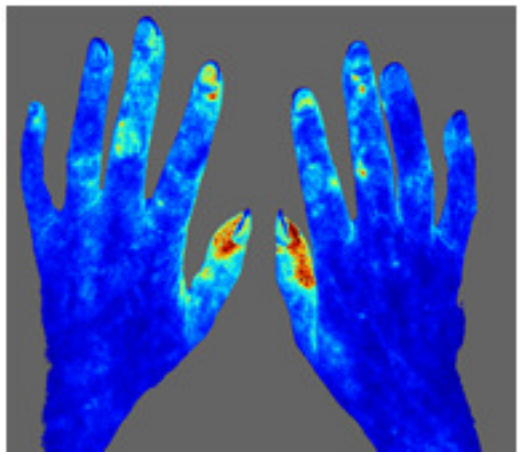
- Knowing what is normal?
- Knowing optical imaging technology
- Calibration
- Develop robust image analysis method
- Testing effectiveness in clinic

Scleroderma Imaging Research (UKCRN Portfolio)

~£200k Grant application to Arthritis Research UK

Manchester University lead – 7 centres in UK – JA Co-I





Wilkinson *et al* 2018: Arthritis and Rheumatology

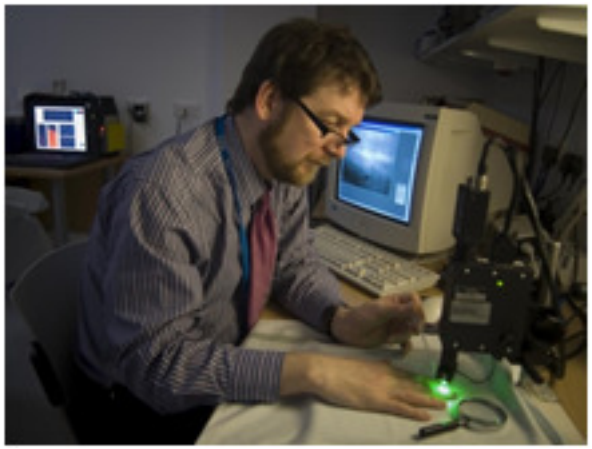
Nailfold capillaroscopy (NFC)

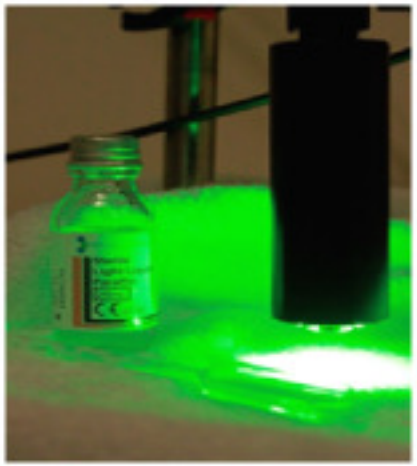
Additional modality:

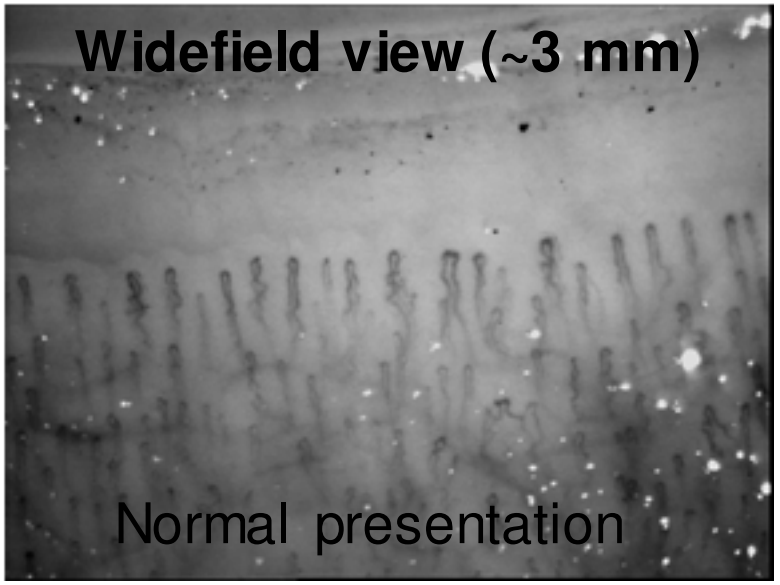
Nailfold Capillaroscopy (NFC) imaging

Capillaroscopy and Thermography combined for Raynaud's / CTD assessments

Nailfold Capillaroscopy (NFC) in CTD

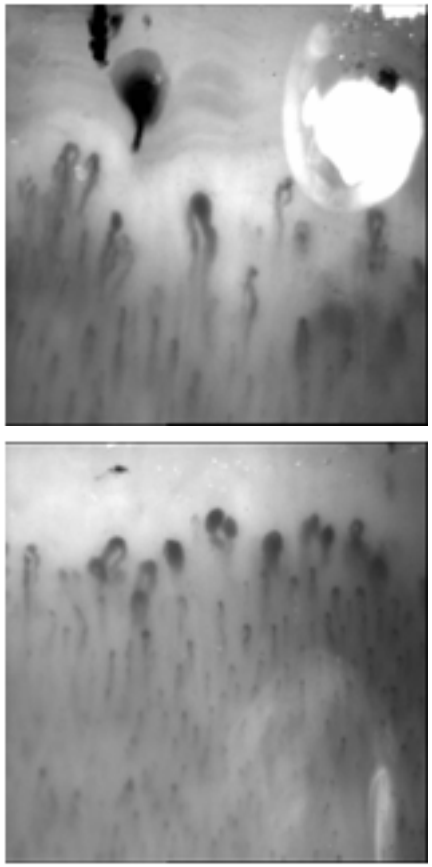






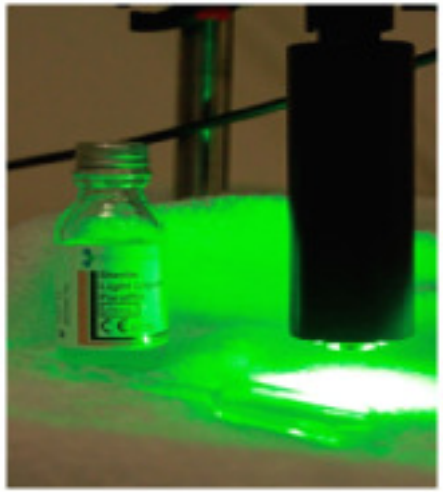
From Allen and Howell 2014 (Physiological Measurement)

Capillaroscopy



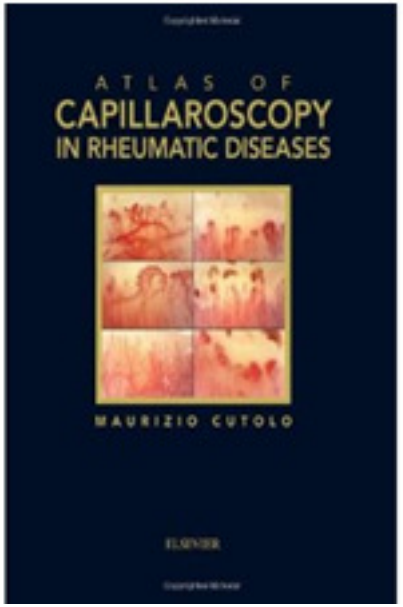
- Microscope study of the capillary bed - often at the finger nailfold region.
- Simple yet powerful optical microvascular technique.
- Can be: fast / formal clinical / or research evaluation.
- Often looking for evidence of small blood vessel disease ('microangiopathy').
- Microangiopathy can be present in connective tissue disease (esp. systemic sclerosis). **Capillaries ~"normal" in primary Raynaud's.**

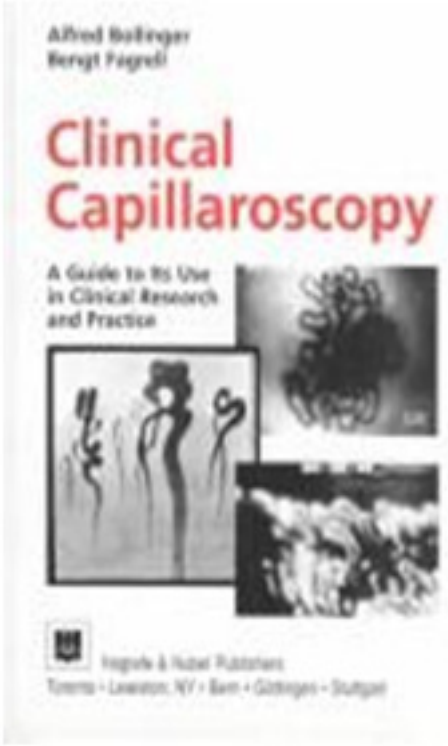
NFC Measurement Method



- Aim to study **8 fingers**.
- **Patient** position – **comfortable and still**.
- Add drop of (light liquid paraffin) **oil** to area of study to improve **visibility**.
- Magnification to achieve **widefield view**.
- **Cold light source**: for colour images (“white”) / B&W images (“green” or “blue”).
- Contact systems: **avoid pressure** on skin.
- Slowly scan across the nailfold, **systematically**.
- Collect images – **need examples** for report.
- We do not study RBC velocities.
- Remove residual oil at end of test (COSHH).
- Typically takes 10-20 minutes.

Capillaroscopy books





Genoa training course (Eular)

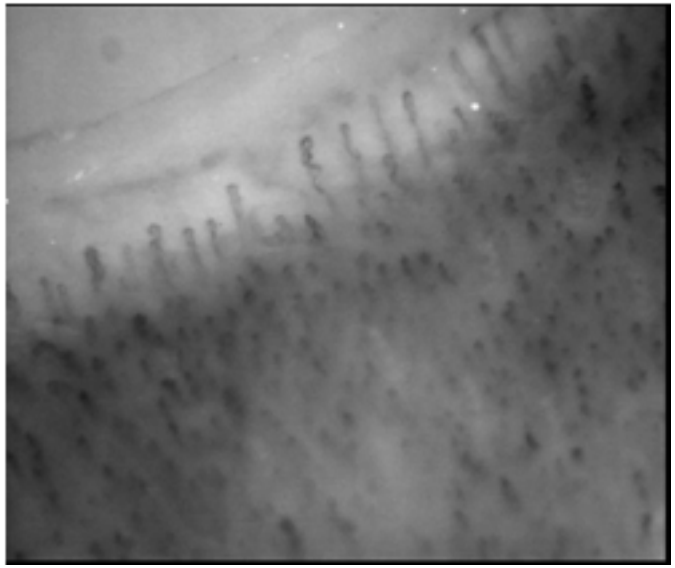
We do <u>combined</u> Thermal Imaging + Capillaroscopy reporting

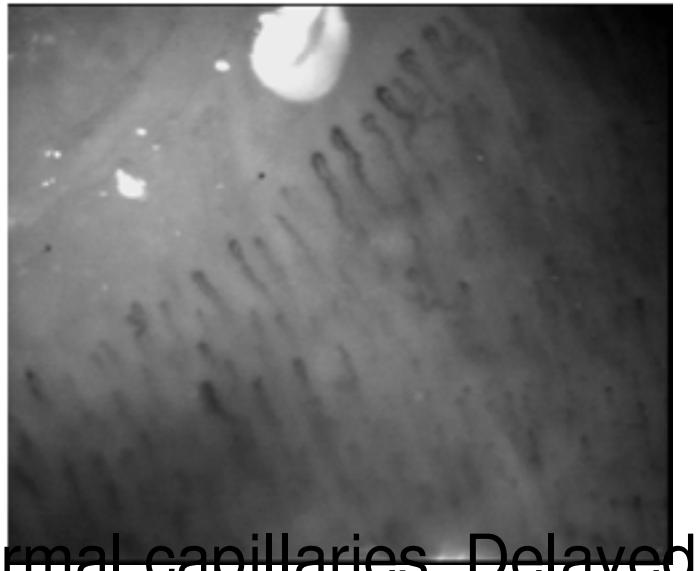
A) Thermoregulatory microcirculation (= Thermal Imaging)

+

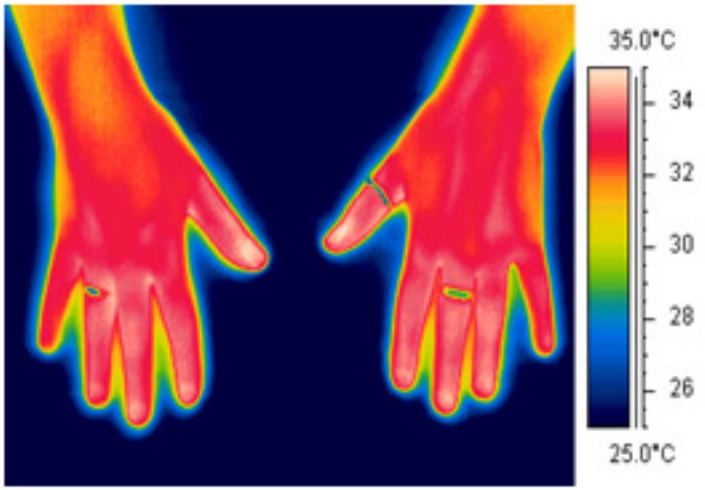
B) Nutritional microcirculation (= NFC)

Reporting: Primary Raynaud's

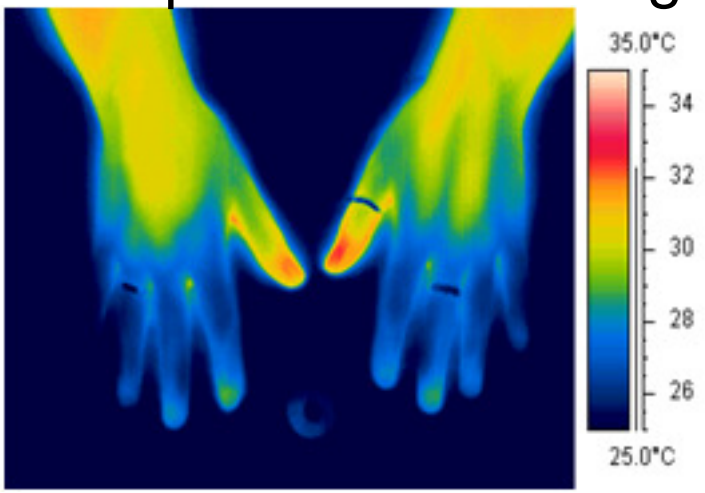




Baseline

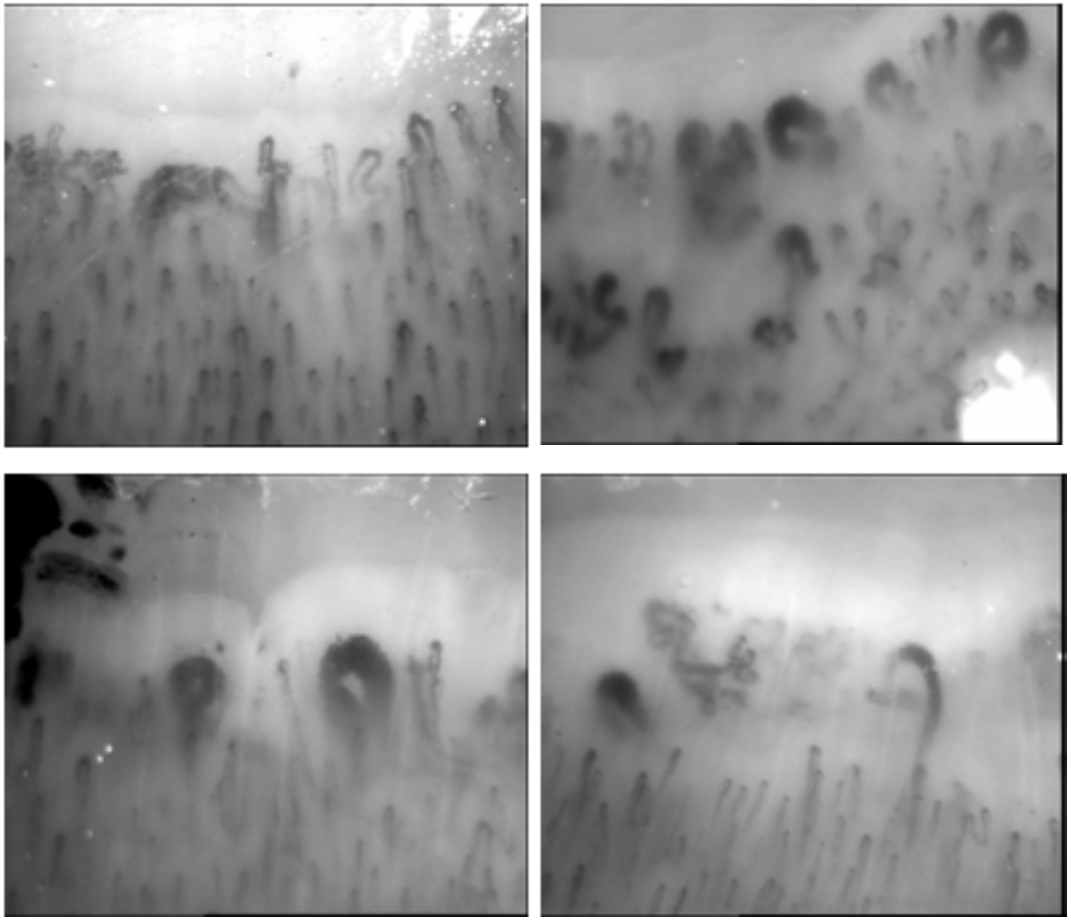


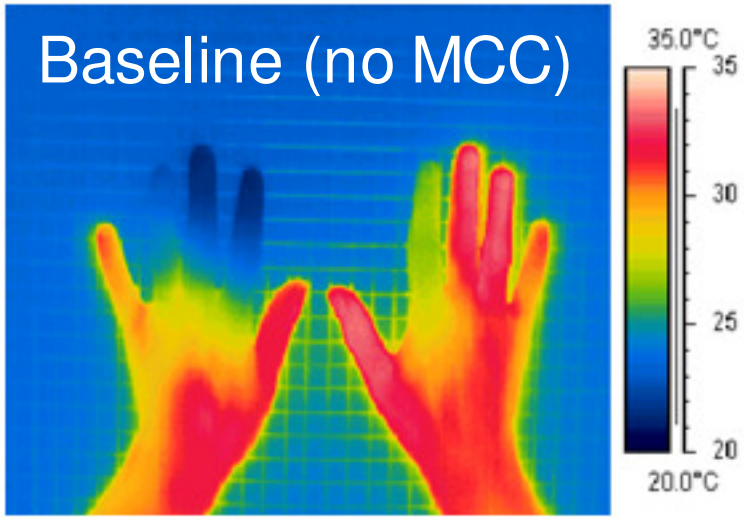
10 min post cold challenge



Normal capillaries. Delayed finger re-warming but symmetrical.

SSc pattern / (secondary) Raynaud's

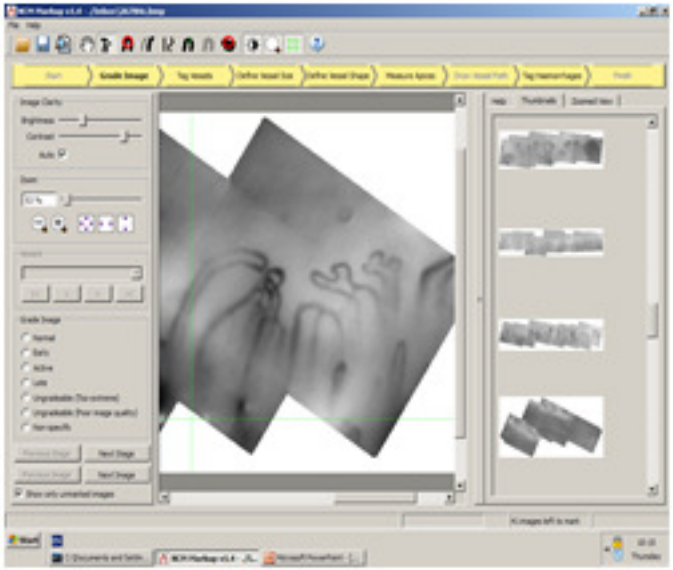




Capillaries abnormal. Abnormal immunology. Asymmetric thermography.

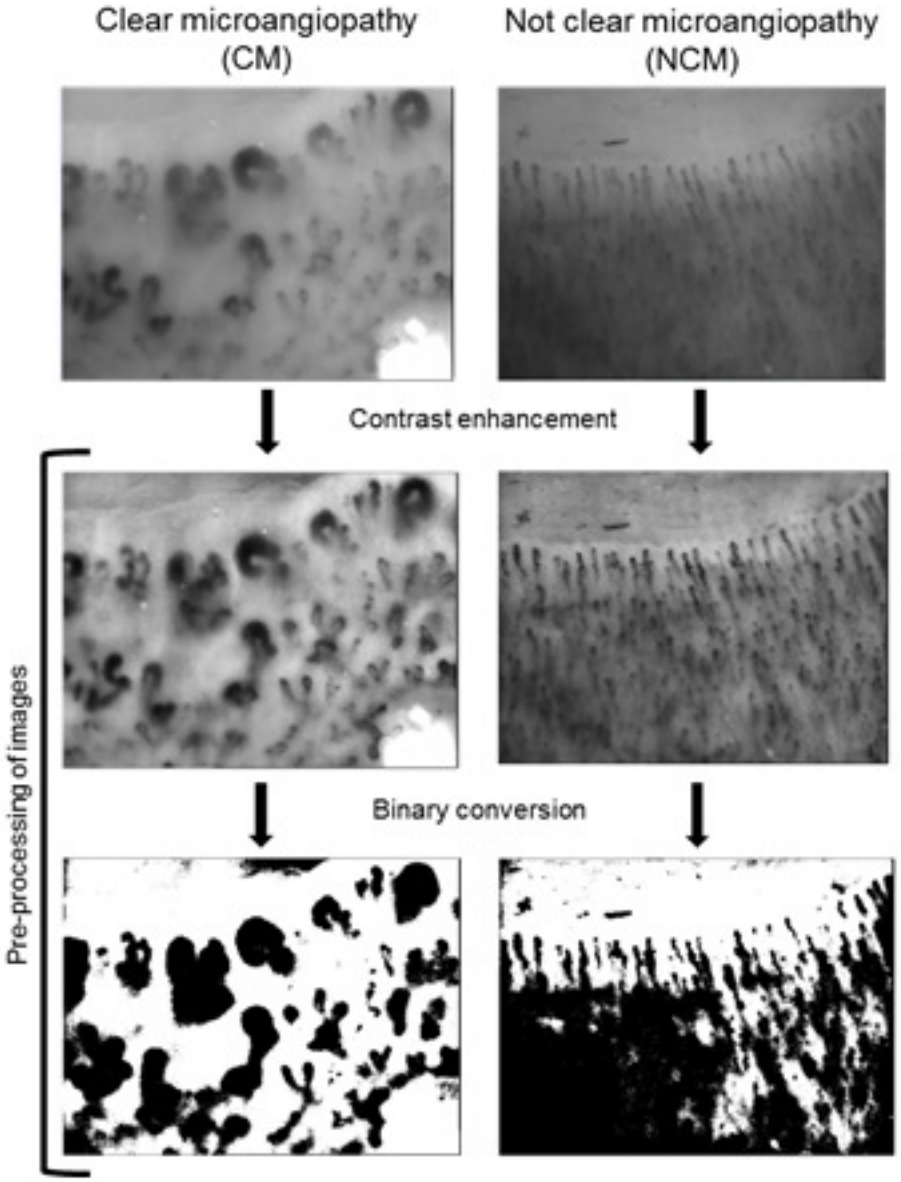
Capillaroscopy research

Manchester University / European Consortium – quantification & agreement between experts:



NIHR i4i device development (Manchester).
Automated image analysis : Fontan and SSc.

Automated image analysis in SSc (**fractals and complexity**):

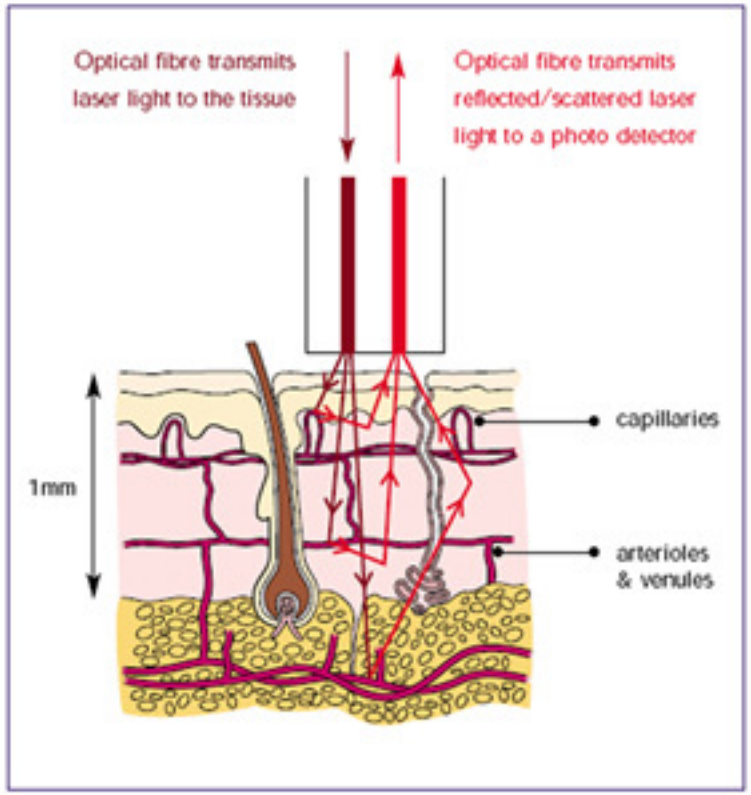


Urwin et al 2016 Physiol Meas

Vascular Optics:

Laser Imaging

Single point blood flow measurement – using laser Doppler flowmetry



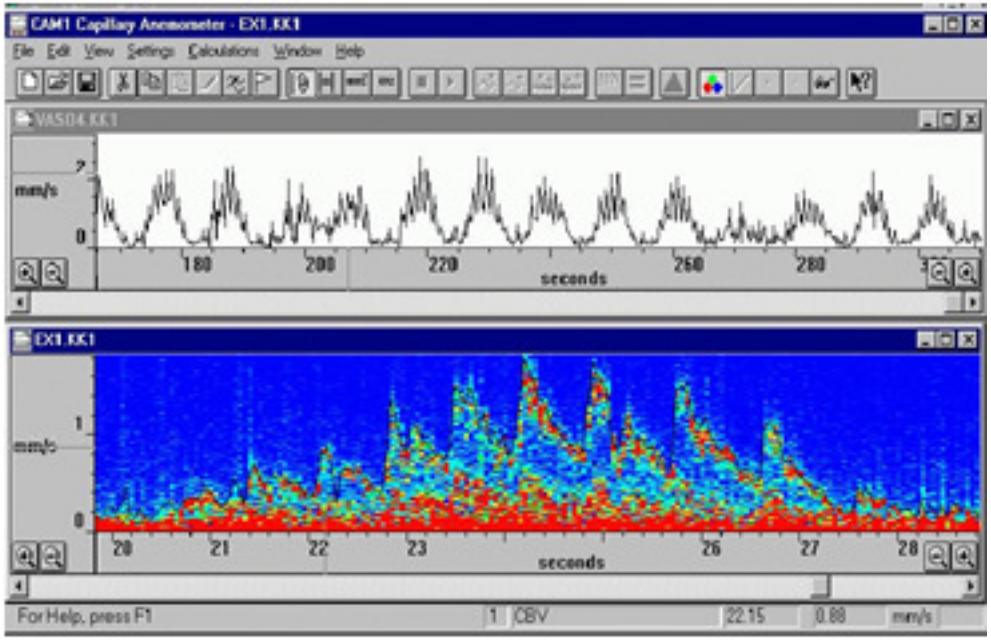
Originally single point measurement system, measuring Doppler shift from moving RBCs (20 Hz – 20 kHz).

Image - Moor Instruments

Laser Doppler flowmetry (single site):

NIR Laser – 780 nm

Skin probe – Wide area



RBC velocities complex, i.e. not always steady flow in capillaries

Single site blood flow measurement

(Stern, Nature, 254:56-58, 1975)

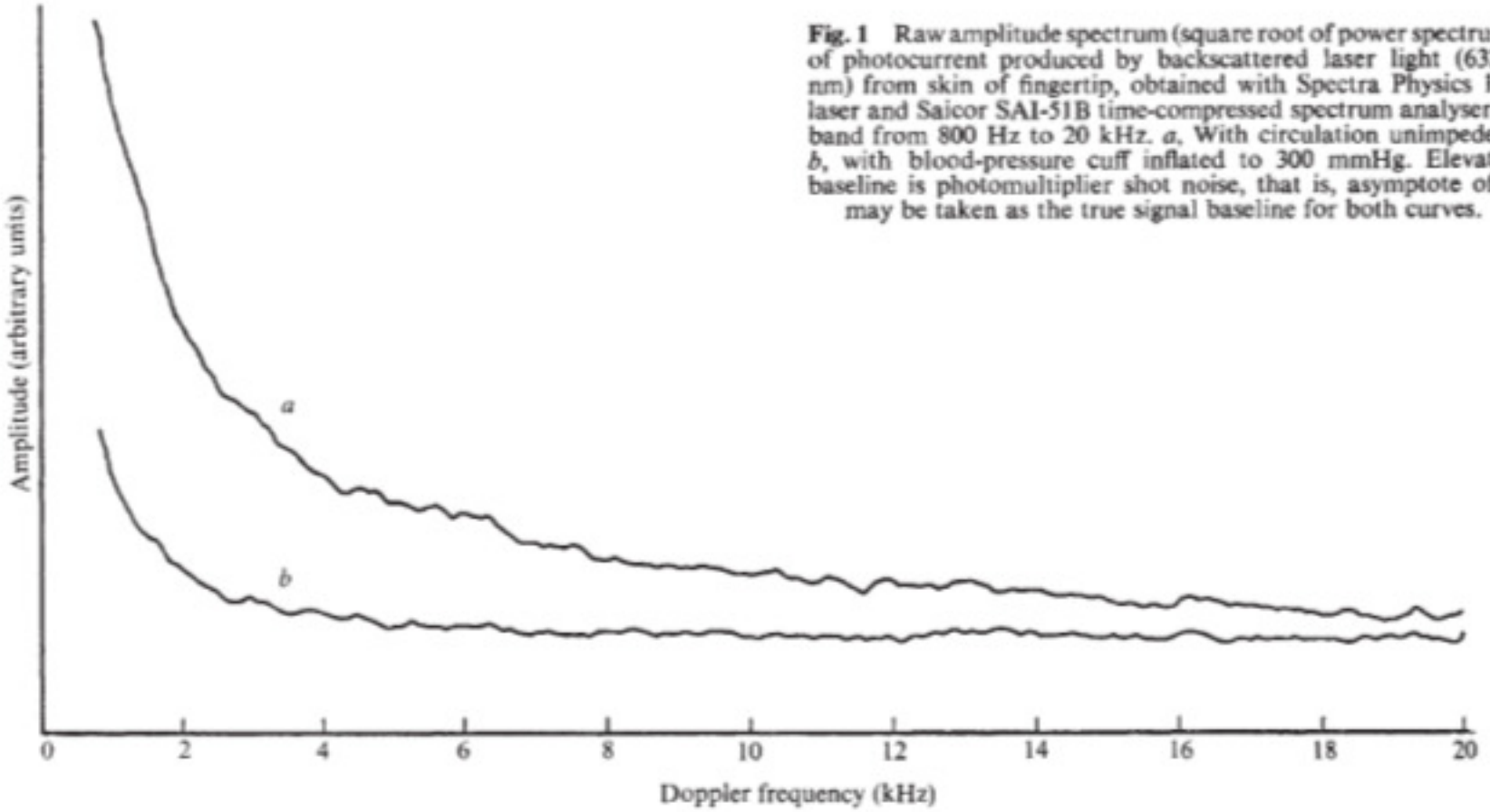


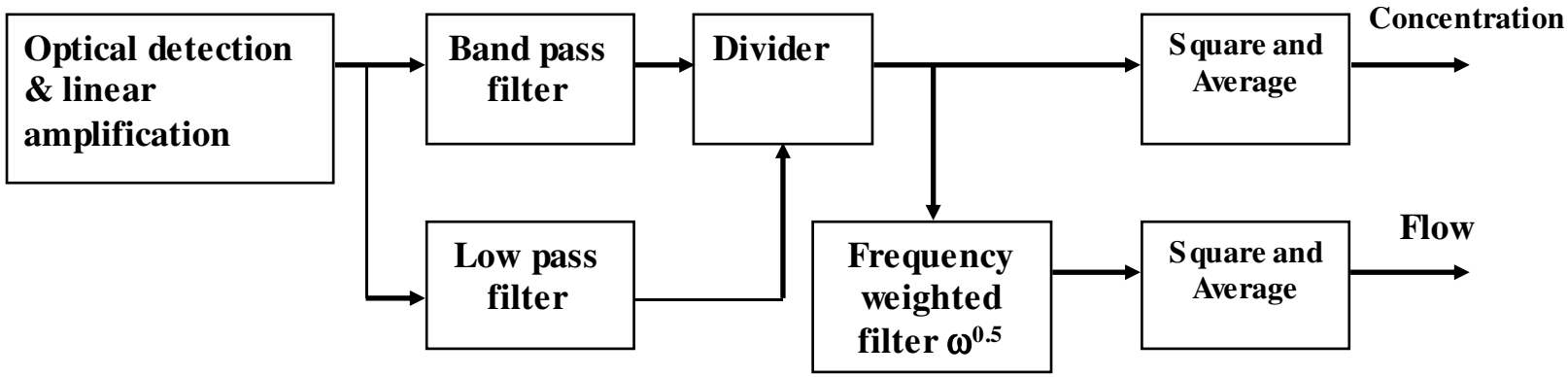
Fig. 1 Raw amplitude spectrum (square root of power spectrum) of photocurrent produced by backscattered laser light (632.8 nm) from skin of fingertip, obtained with Spectra Physics 124 laser and Saicor SAI-51B time-compressed spectrum analyser in band from 800 Hz to 20 kHz. *a*, With circulation unimpeded; *b*, with blood-pressure cuff inflated to 300 mmHg. Elevated baseline is photomultiplier shot noise, that is, asymptote of *b* may be taken as the true signal baseline for both curves.

$$\text{Concentration} = \int_{\omega_1}^{\omega_2} P(\omega)d\omega$$

$$\text{Flux} = \int_{\omega_1}^{\omega_2} \omega P(\omega)d\omega$$

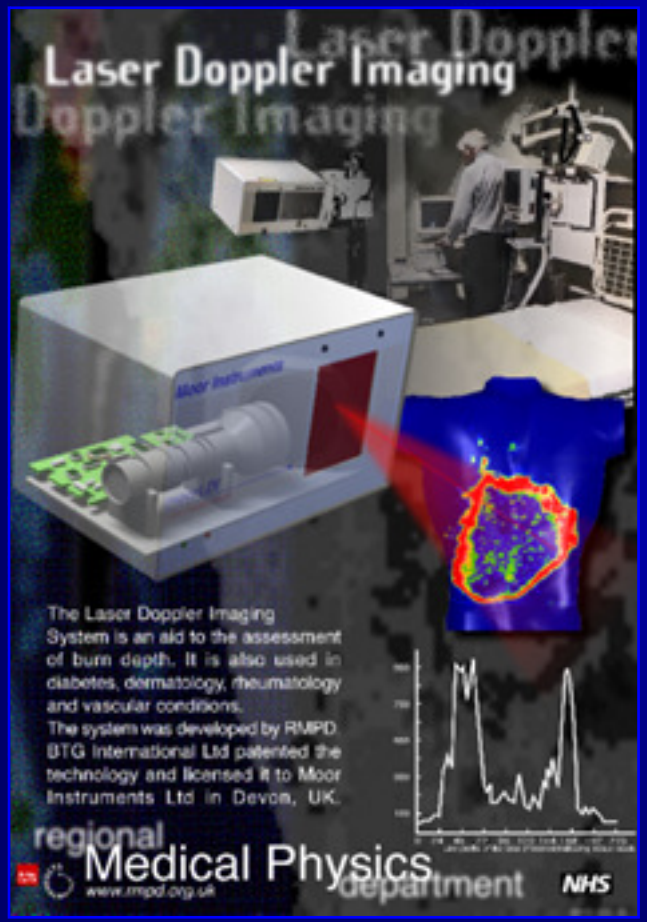
Processing of laser Doppler signals

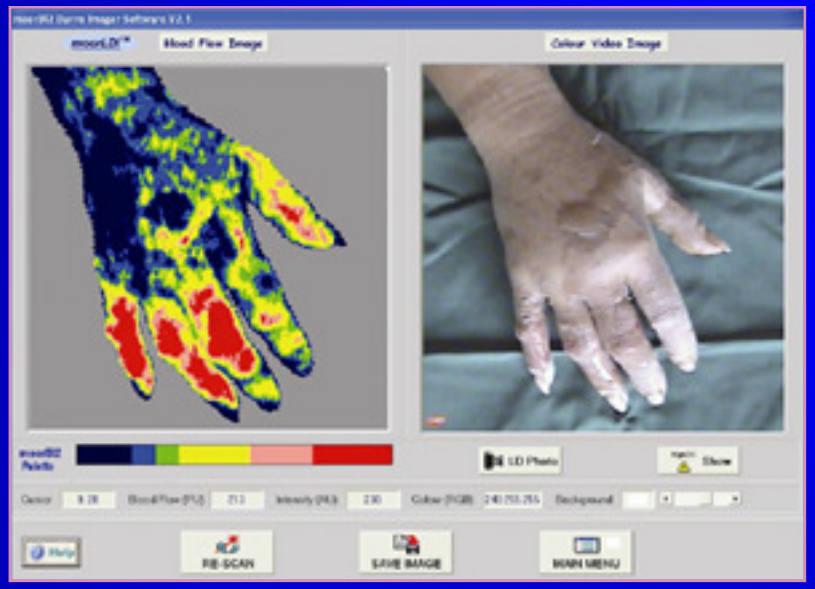
Various approaches used …

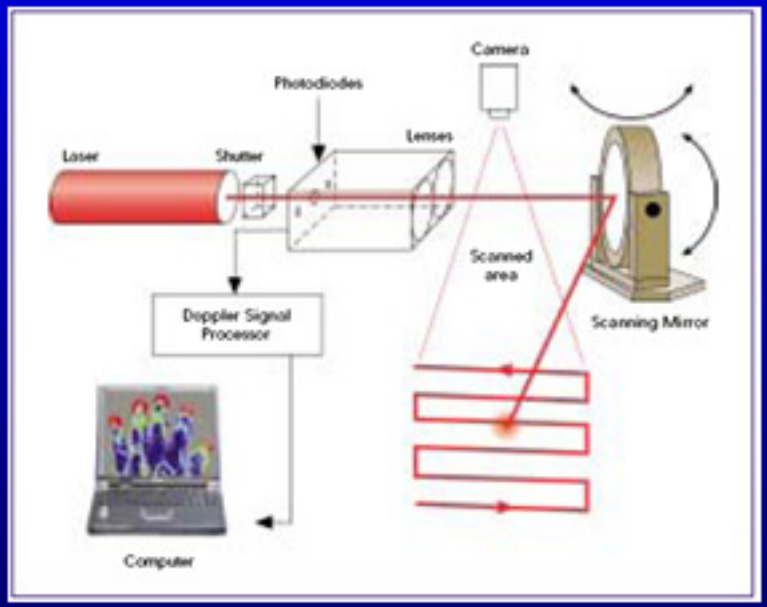


Beclaro (1994), Laser Doppler, Med-Orion.

Laser Doppler imaging

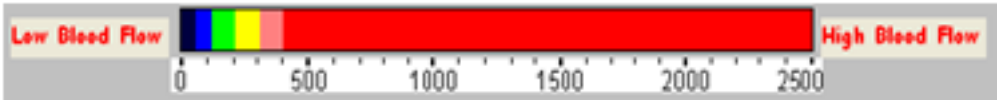




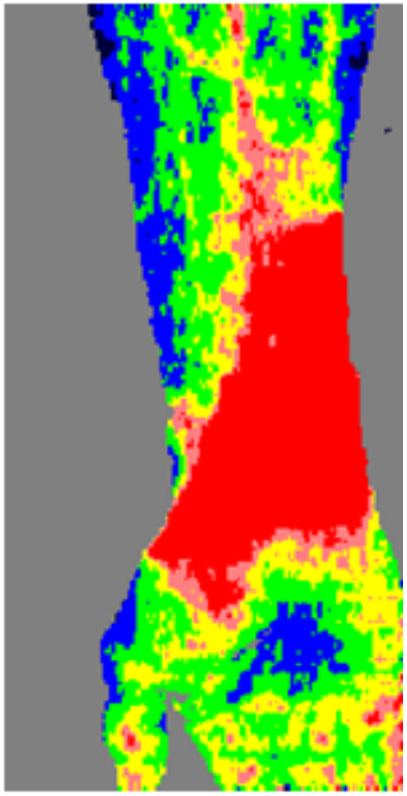


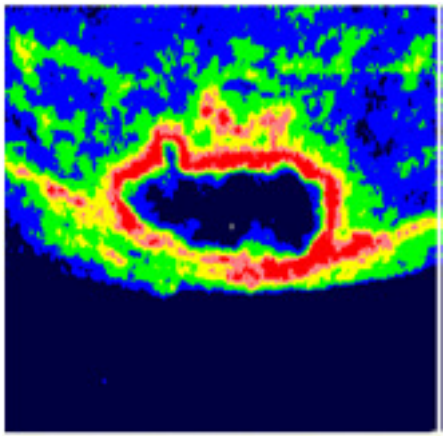
Microvascular (skin) blood flow images

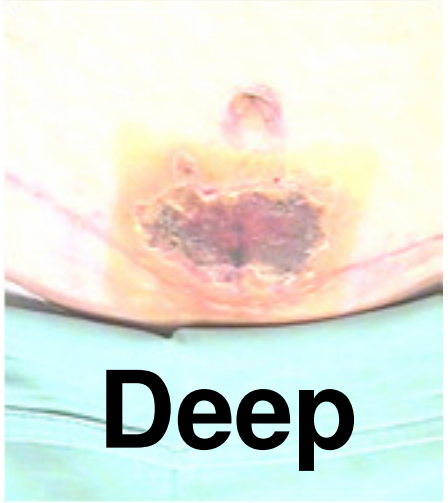
Laser Doppler Imaging: Burn depth



= Knowing the physiology

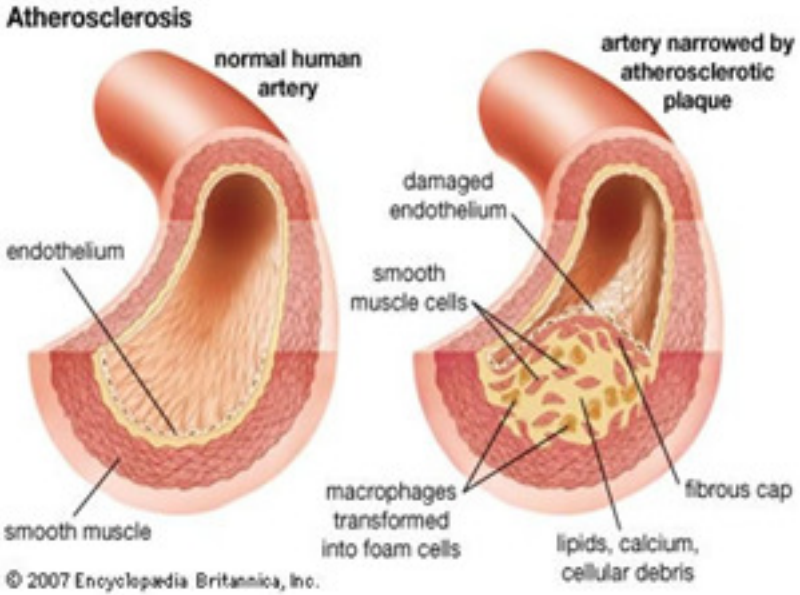


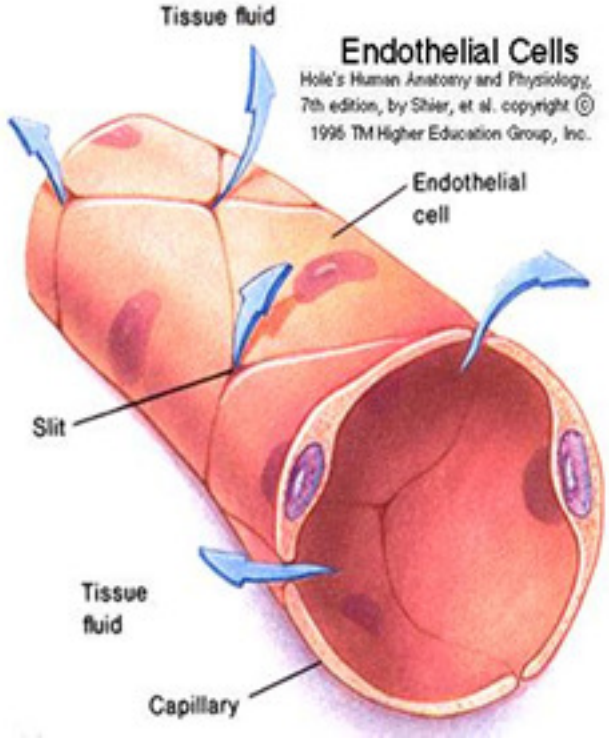




Allen and Howell 2014

Endothelium (macro- and micro-circulations)



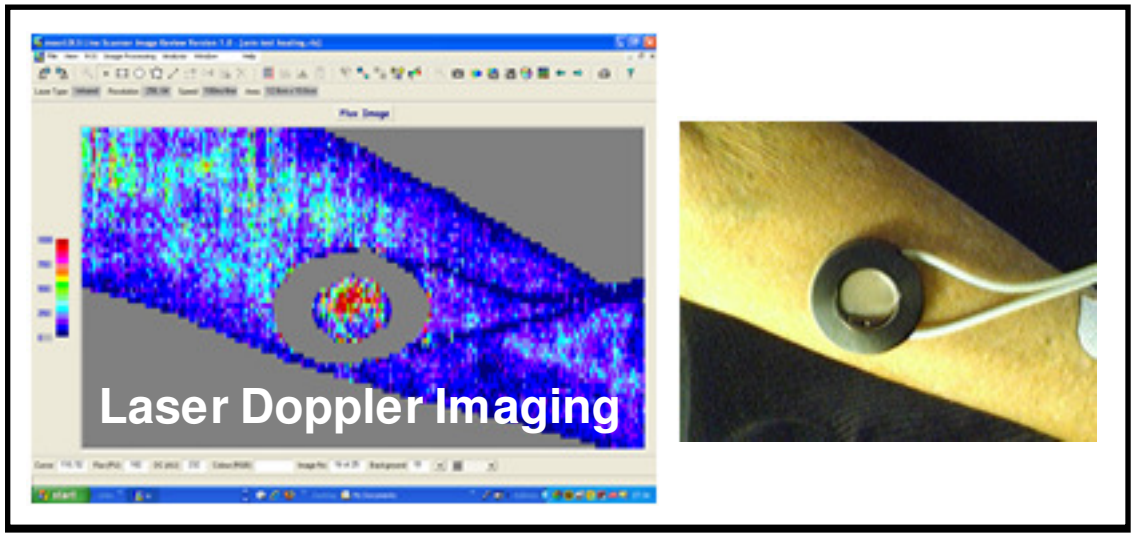


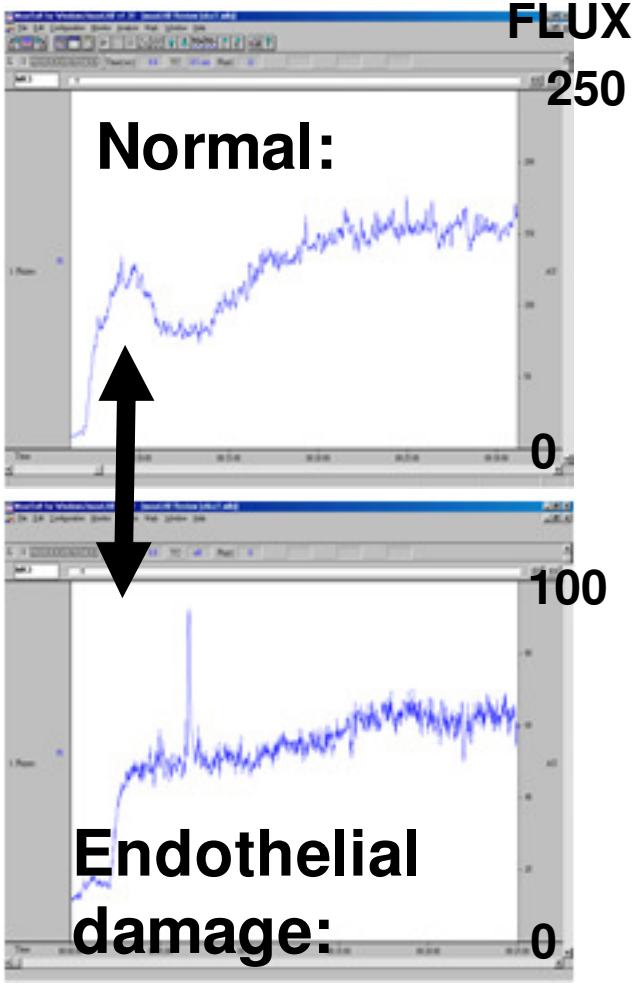
Arteries

Capillaries

Laser Doppler: Thermal hyperaemia

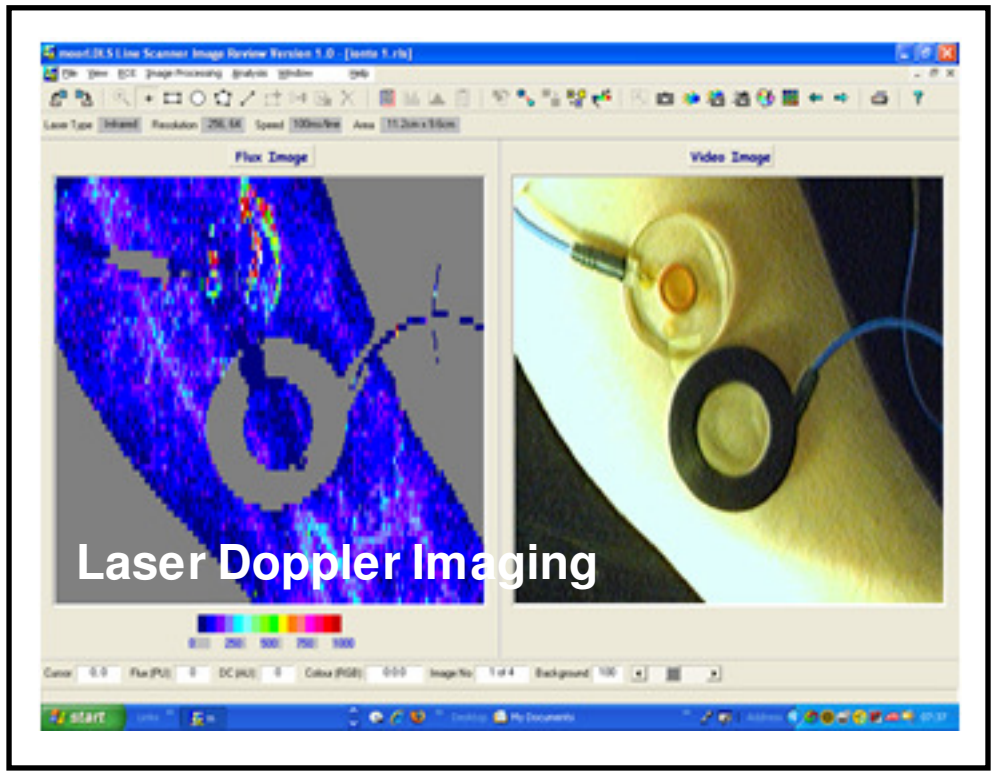
Microvascular Endothelial Function assessment (skin to 41 °C for 30 min)

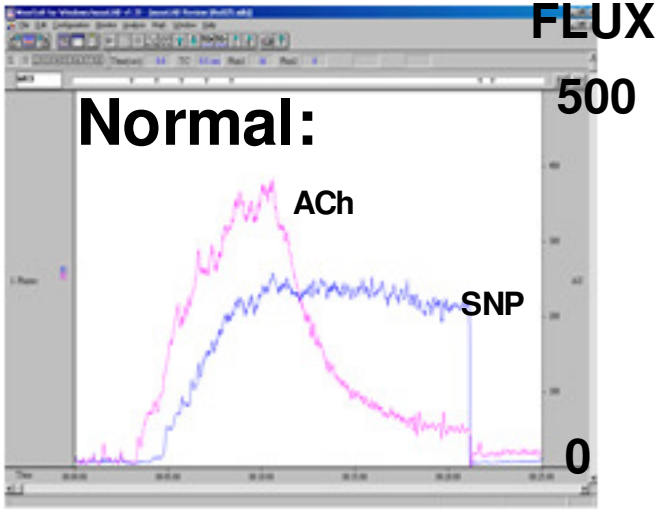


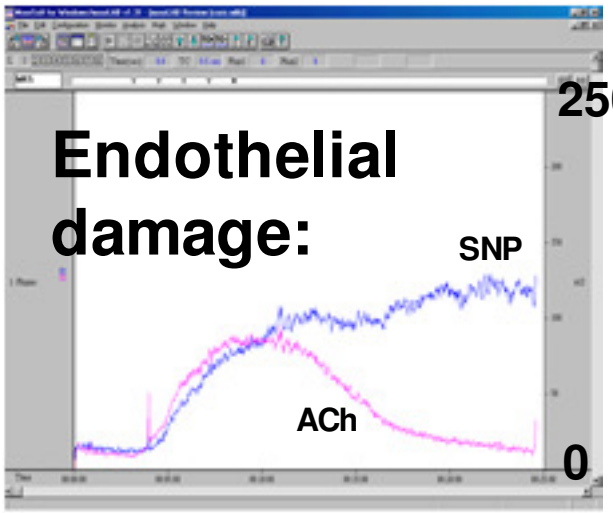


Laser Doppler: Iontophoresis

Microvascular Endothelial Function assessment (both ACh + SNP)

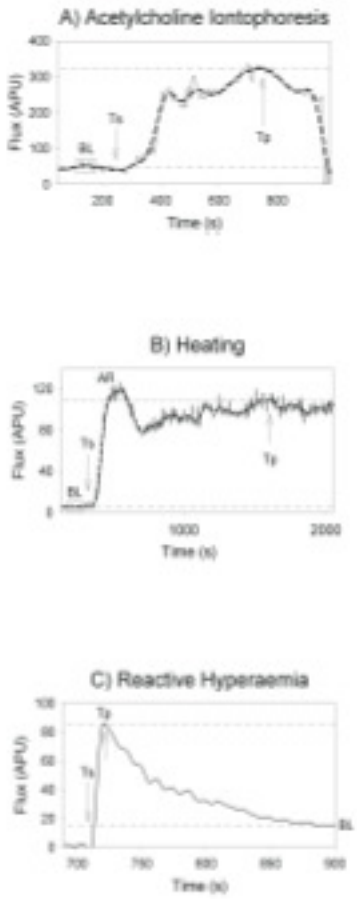


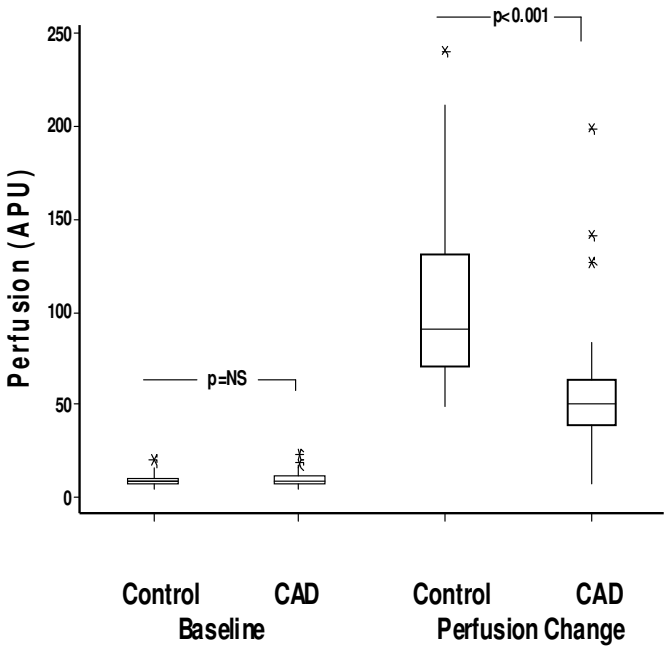


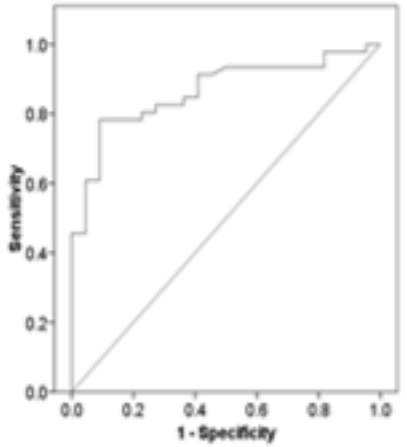


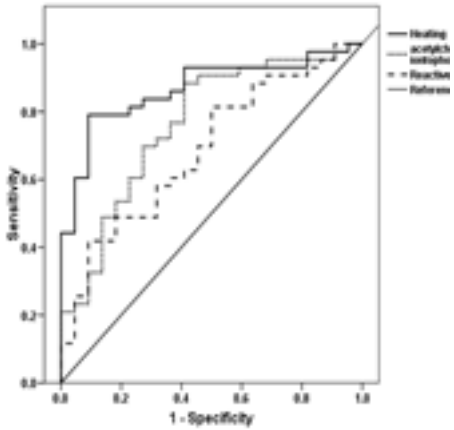
Can assess endothelial *dependent* (Ach) and *independent* (SNP) responses

Endothelial Function – Laser Doppler









Repeatability data :

Agarwal *et al*

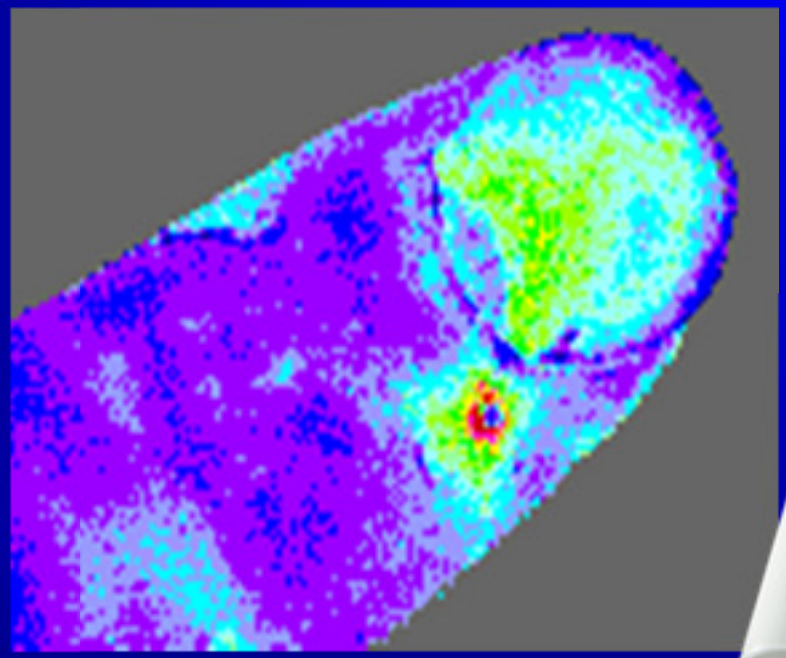
Physiol Meas 2010;31:1-11

Clinical paper - CAD patients :

Agarwal *et al*

Microvasc Res 2012;84:55-9

Laser speckle imaging (Moor Instruments)



From Moor Instruments website

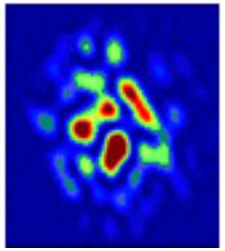
- Full field imaging
- Indirect measure of fluctuations
- Reduction in spatial resolution, spatial averaging

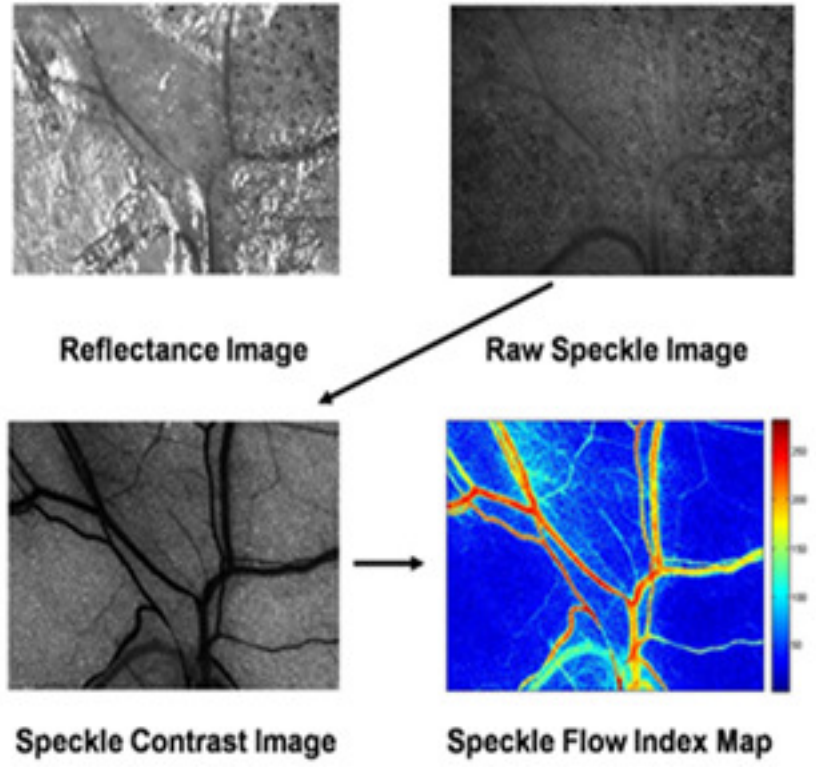
Laser speckle (granularity)

Random pattern generated, changes with blood flow:

Fast flow (i.e. blurred with contrast reduced). Low flow = high contrast.

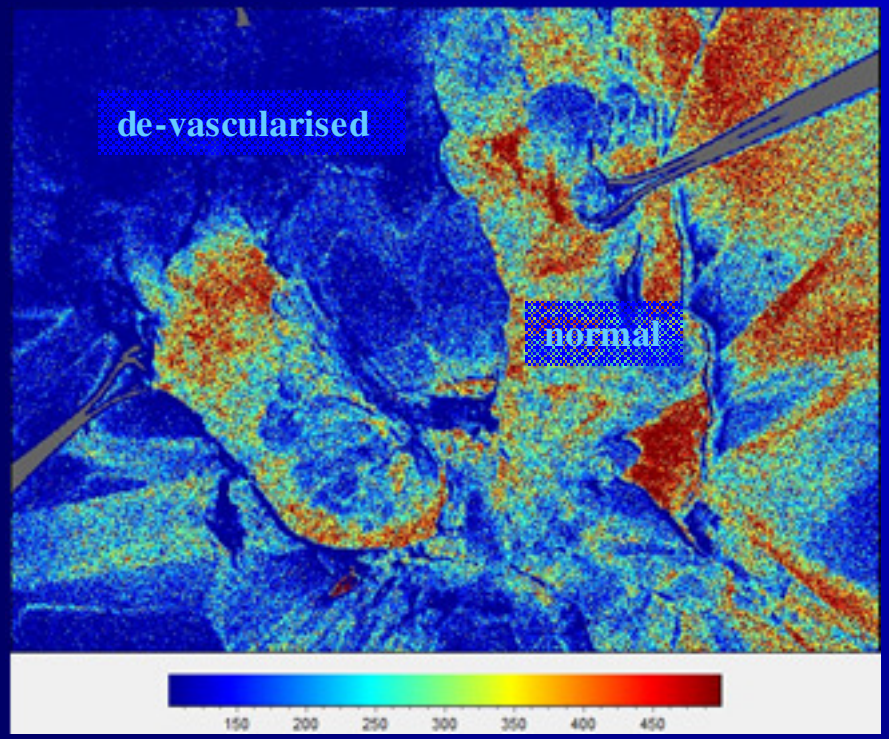
Contrast convert to image of "flow".

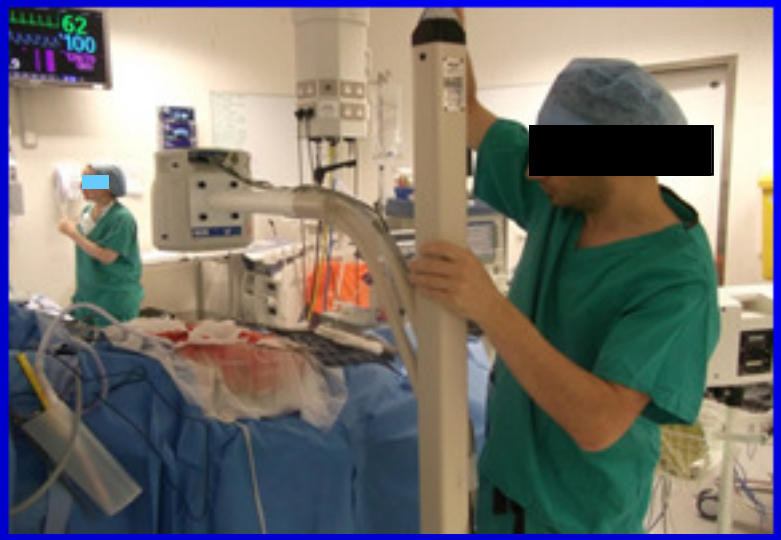


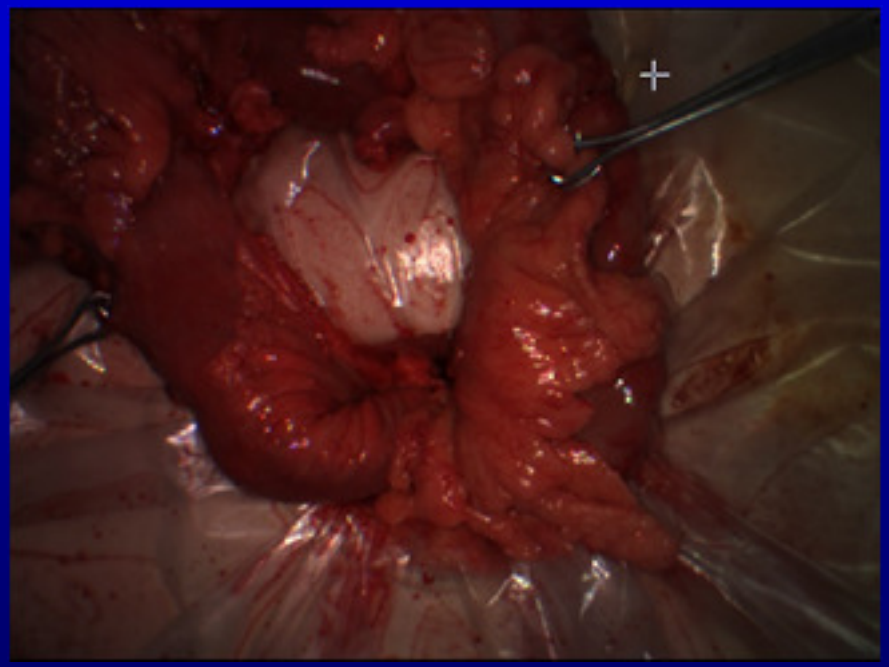


Can measure at 25 fps!

Test development: Laser Speckle Imaging







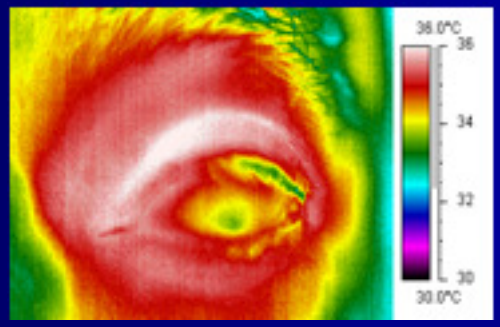
From Di Maria *et al* 2017

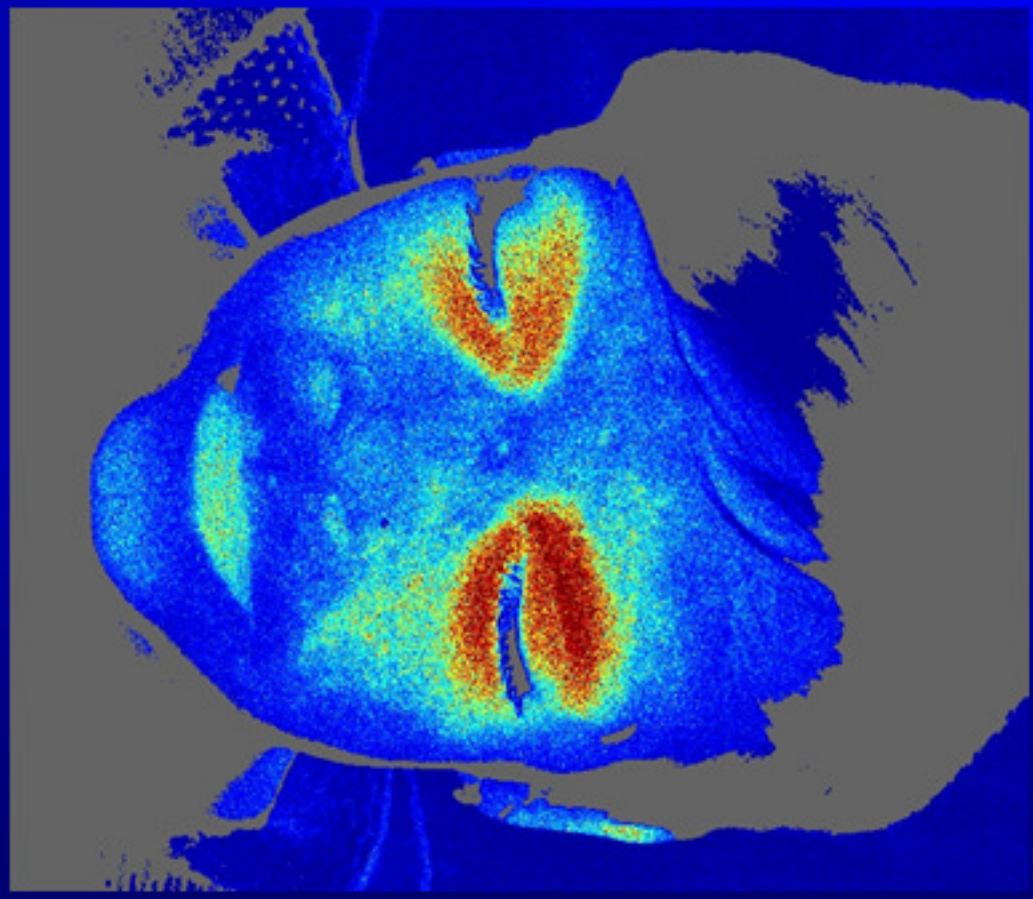
Normal bowel flux: 340 AFU

De-vascularised bowel flux: 67 AFU

Laser speckle imaging of tissue viability: Thyroid eye disease – Active inflammation

Thermal image



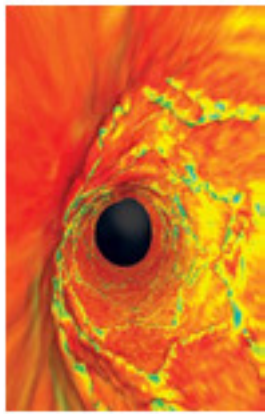


Vascular Optics:

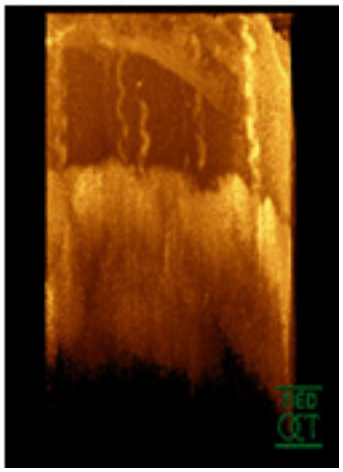
Other optical imaging techniques with capability for microvascular assessment

Optical coherence tomography (OCT)

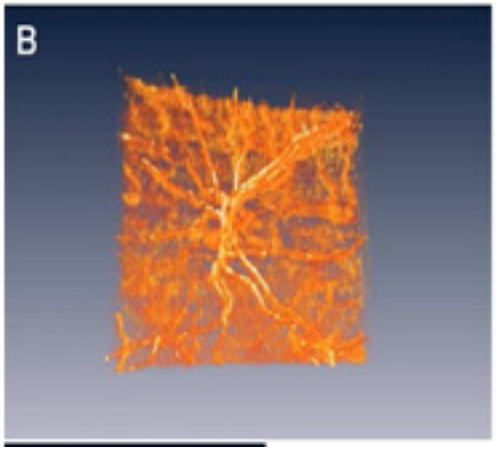
- Typically uses infrared light. *Interferometry*.
- High resolution.
- Tissue discontinuities / micro-structures.



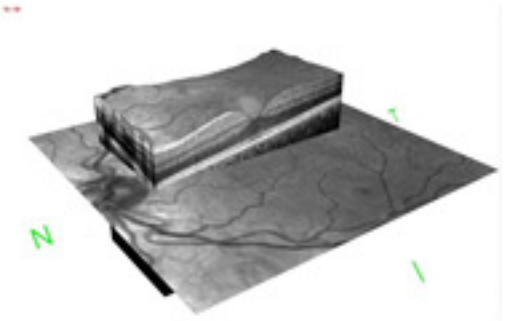
Coronary Artery wall composition



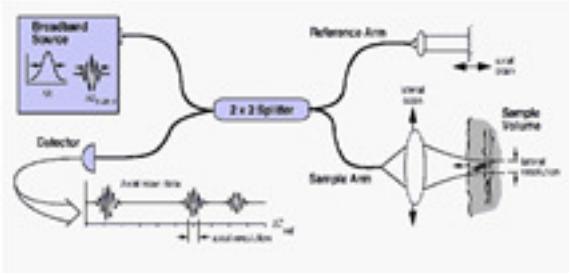
3D skin (~mm^3)



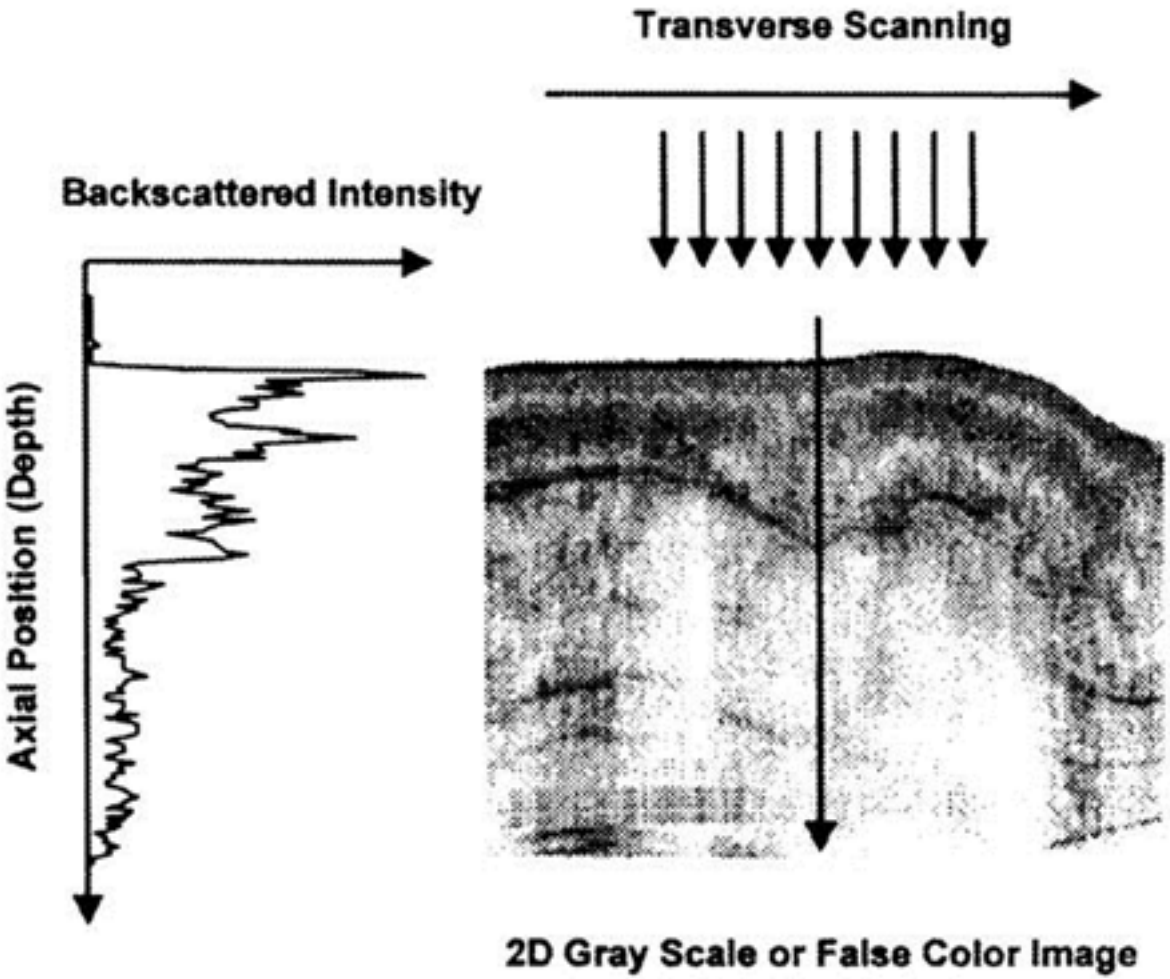
OCT Doppler blood flow



Eye



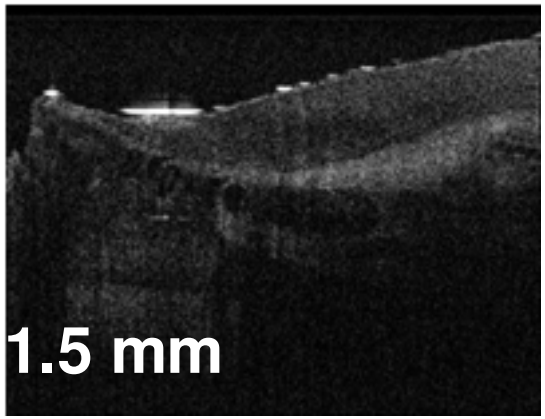
Construction of image

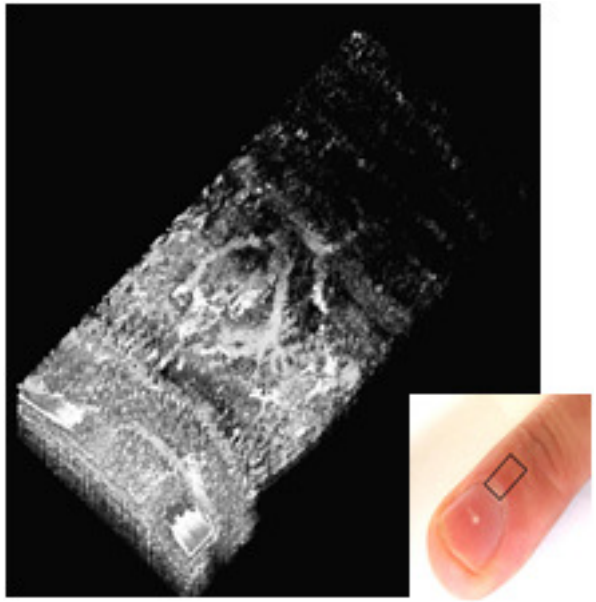


Source of contrast: refractive index variations

Frame rate for OCT systems typically 4 to 8 fps, but can be x10 here.

OCT Skin imaging





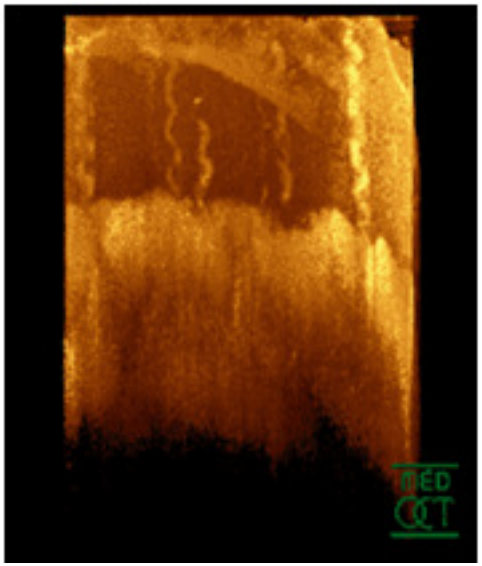
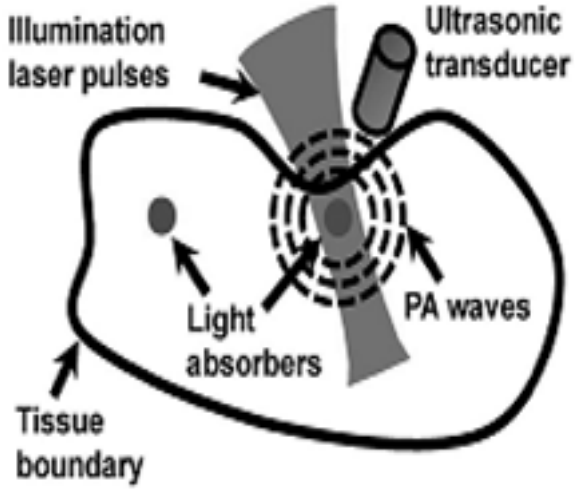
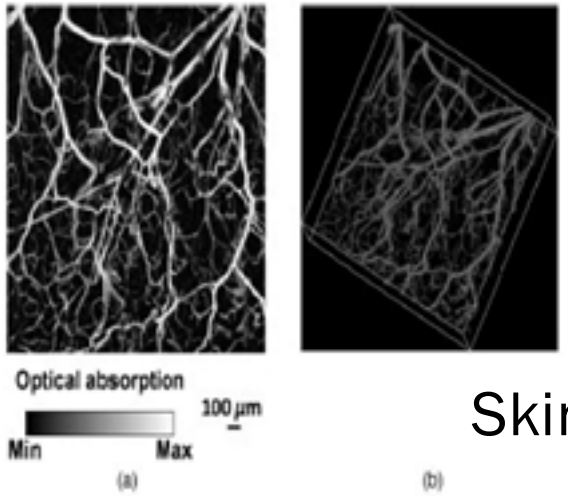
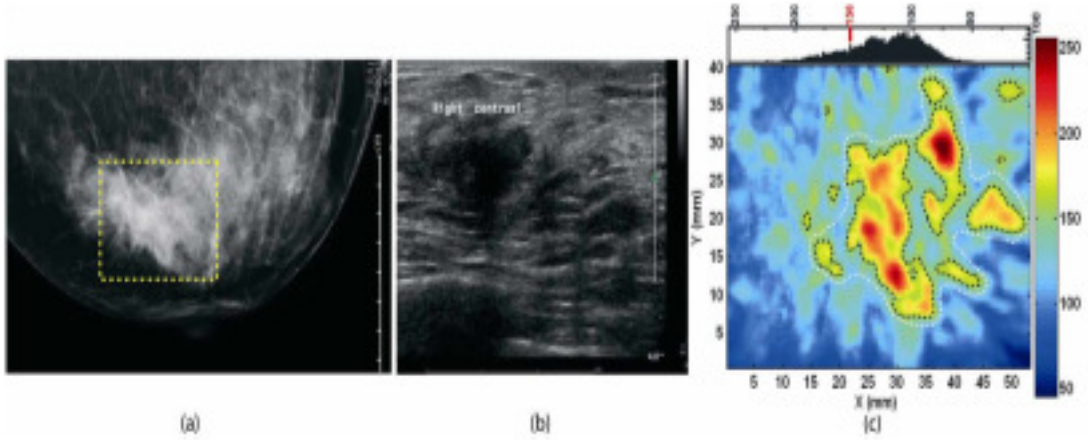


Photo-Acoustic Tomography (PAT)



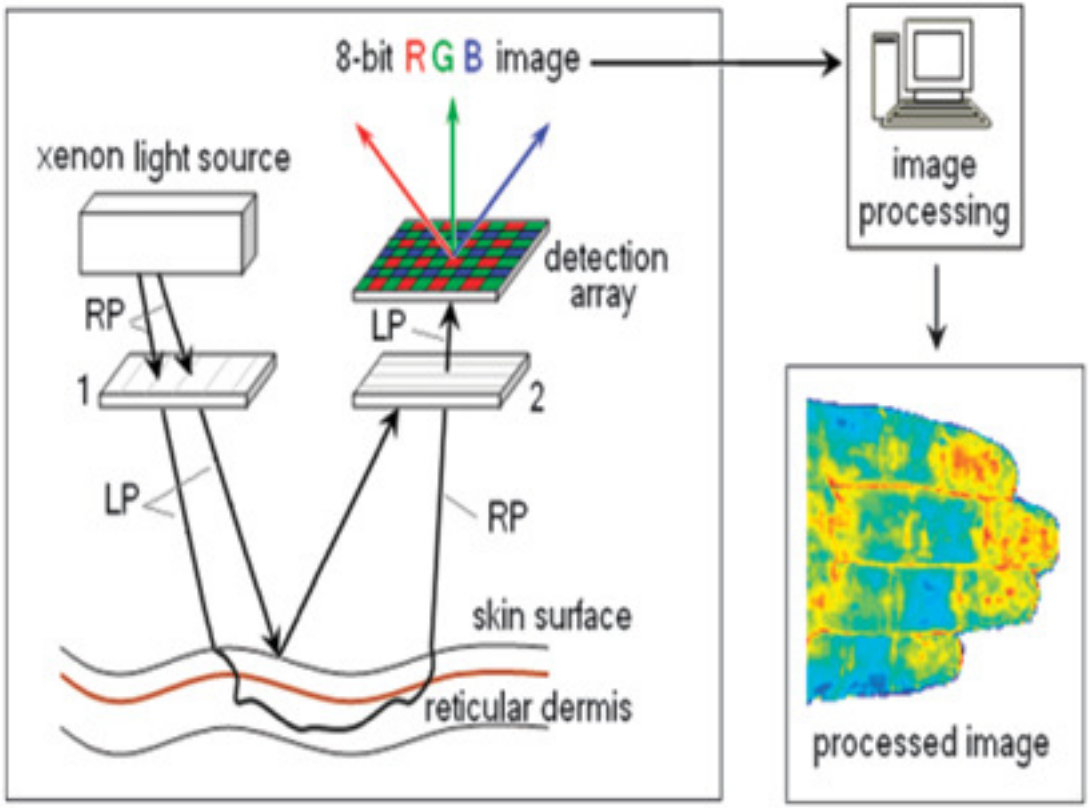


Skin

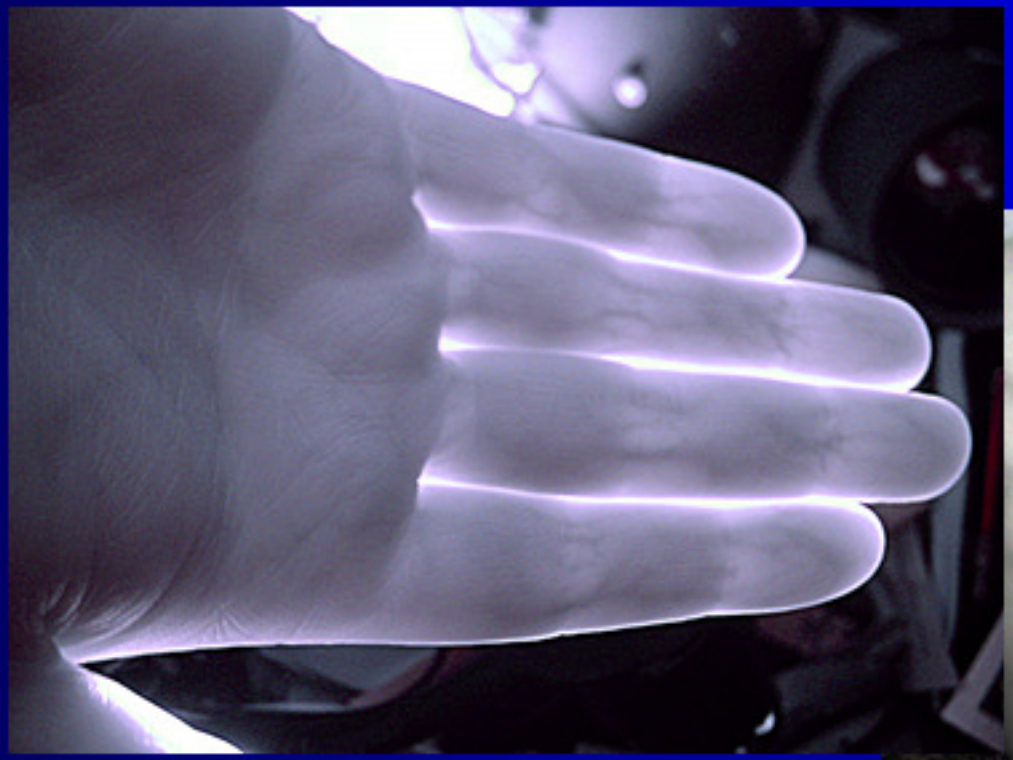


Breast cancer

TIssue Viability Imaging (TIVI): Skin RBC concentration



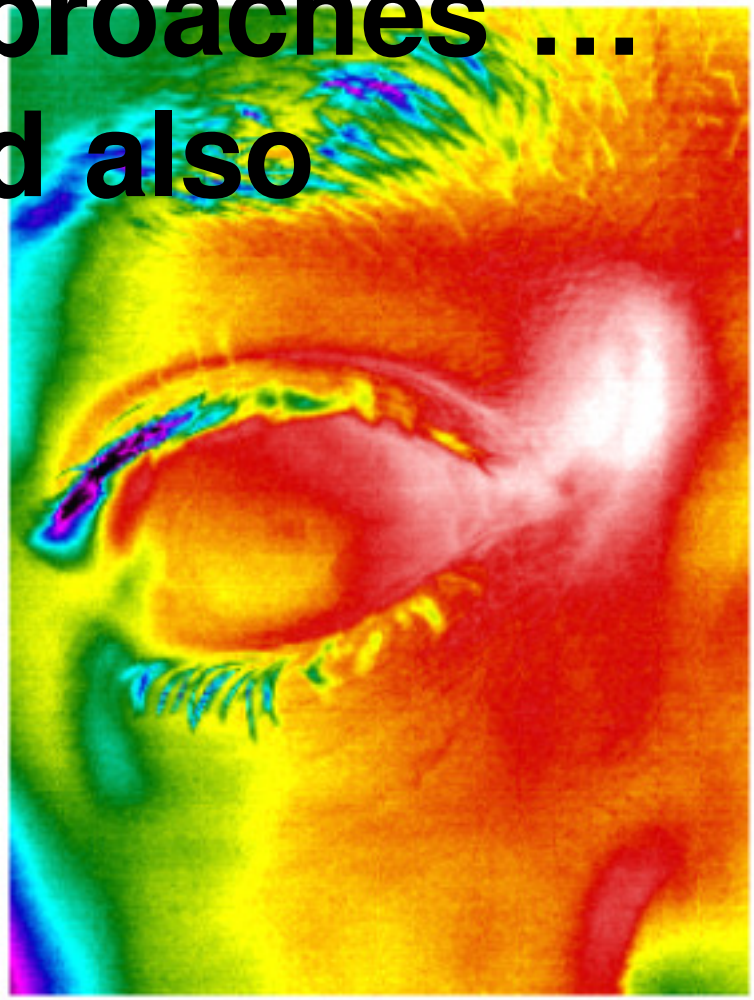
Near infrared (NIR) Imaging



Short wave infrared (SW IR) Imaging

Berlin Heart (VAD) : blood clot formation detection?

Imaging techniques often start from basic spot measurement approaches … consider PPG and also Tissue Oxygen.



Optical Tissue Viability

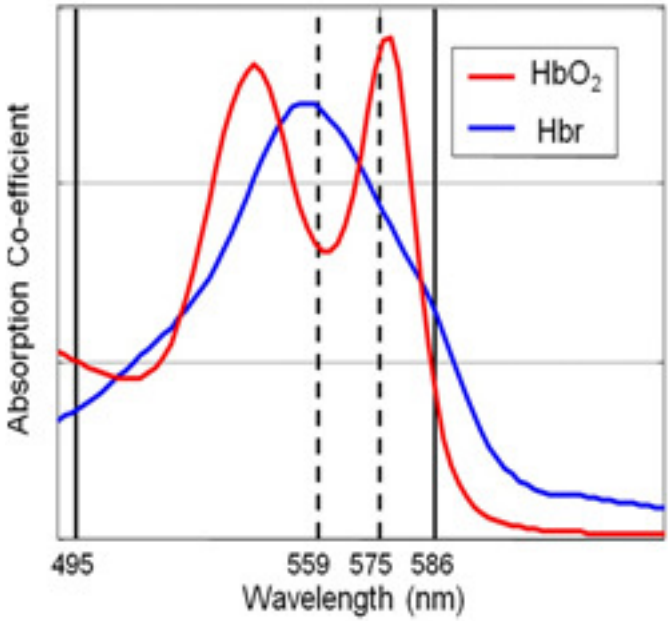
assessed using

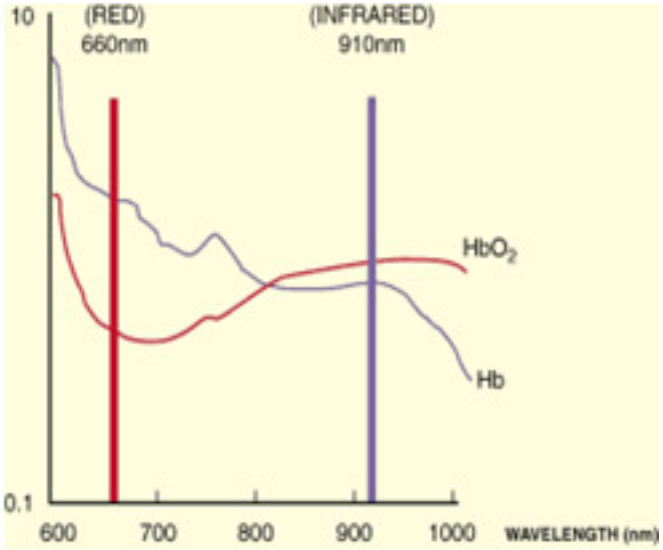
Tissue Oxygen Saturation (TOS)

Tissue Oxygen Saturation measurements

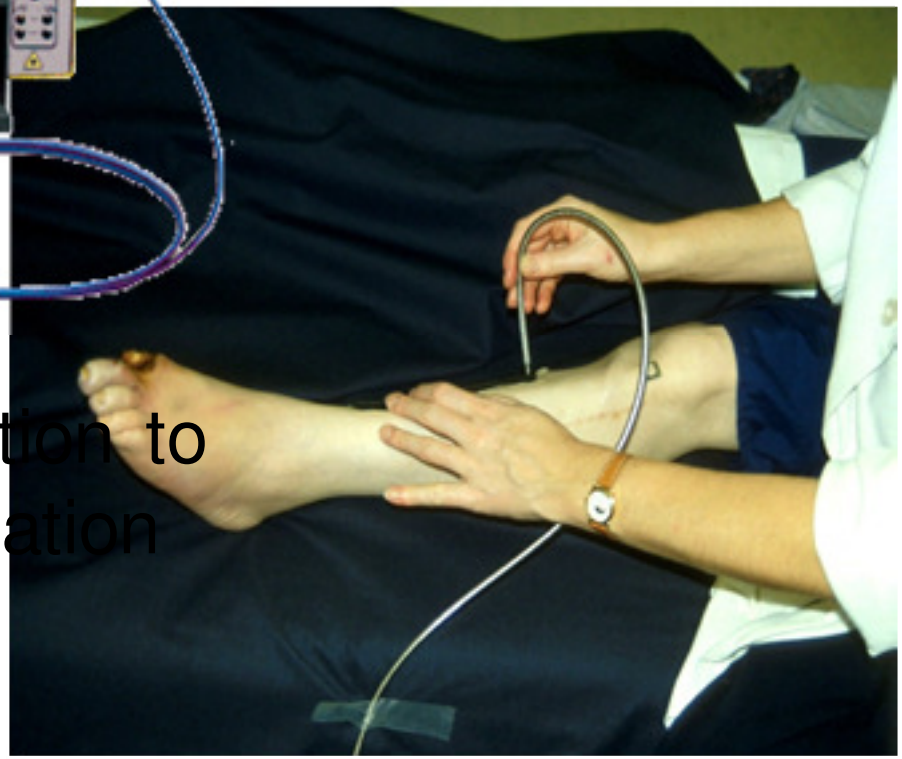
Absorption spectra continued...

Oxygenated Hb (HbO_2) has a different absorption spectrum than de-oxygenated Hb (Hb). Landmark 805 nm (an isobestic wavelength).



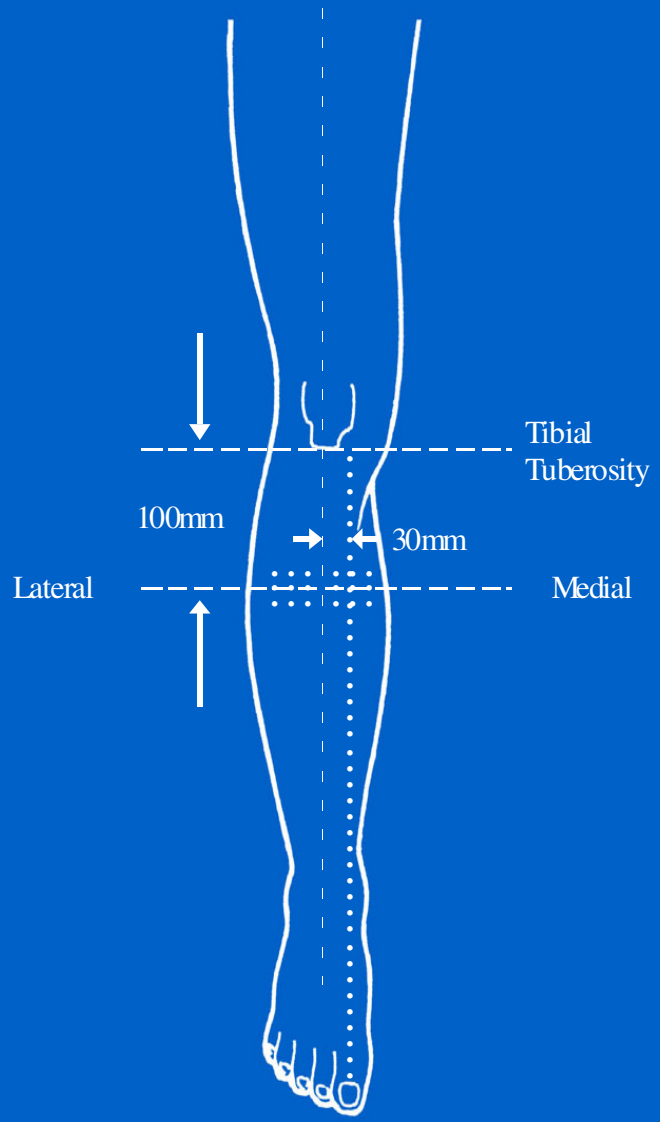


Amputation Level : BK or AK ?

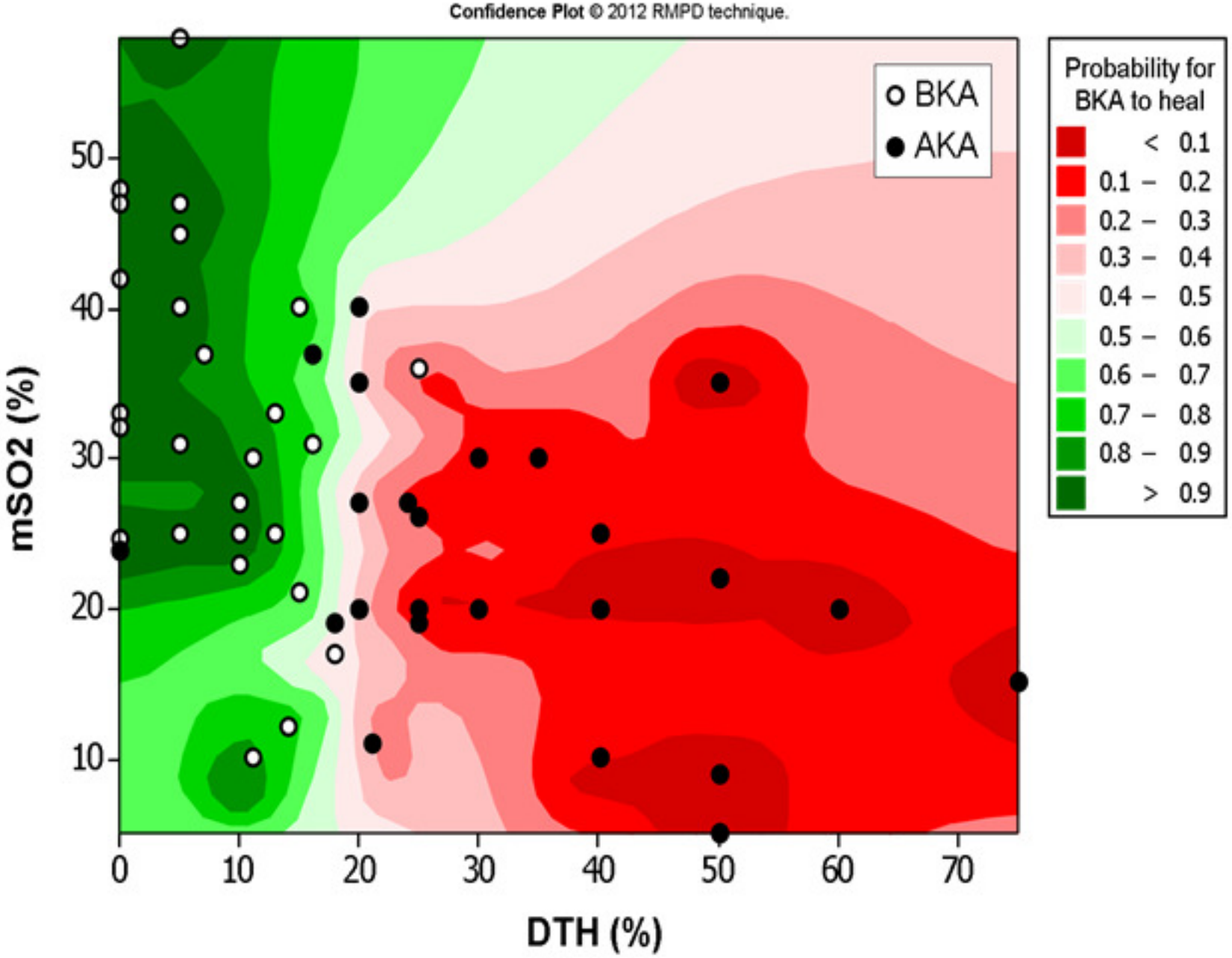


Measuring tissue oxygenation to determine level of amputation

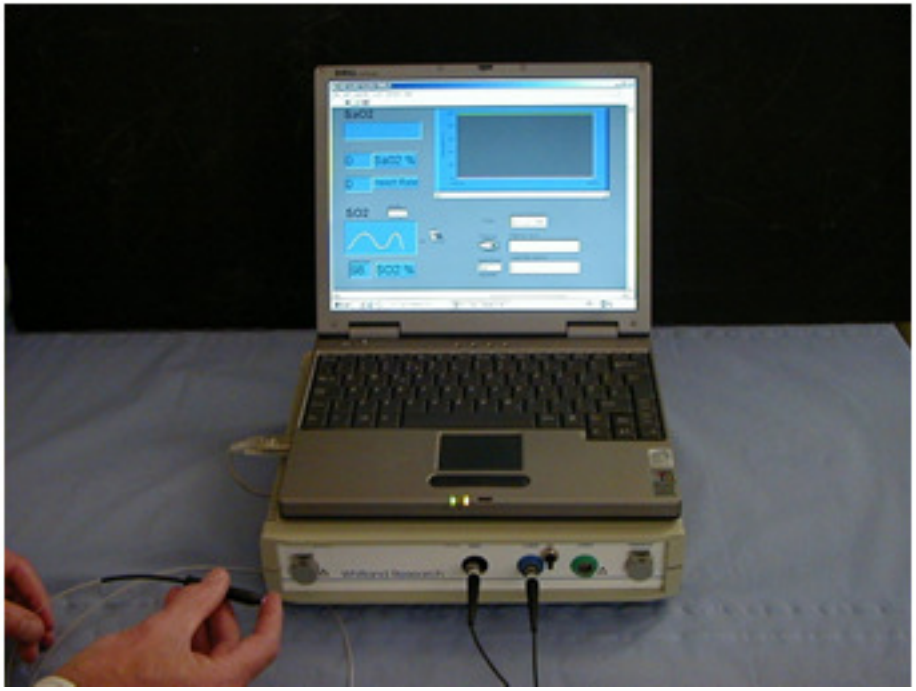
Sites for SO_2 measurements for AK/BK amputation level assessments



Amputation level prediction 2007-2011



Pressure Ulcers:
Risk (NHS Thermometer of care)



Four categories – Type 1 is reversible: non-blanching erythema

Scope for optical assessment?

Scope for imaging too?

Scope for s?

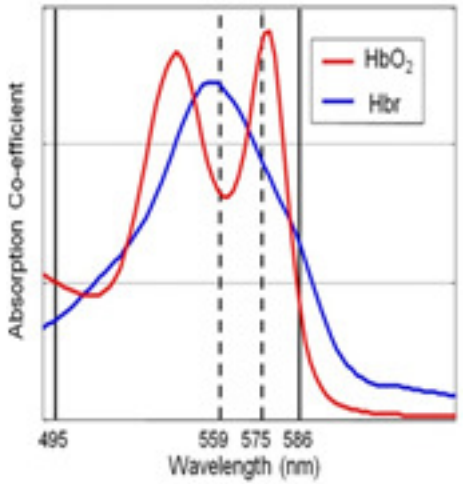
1

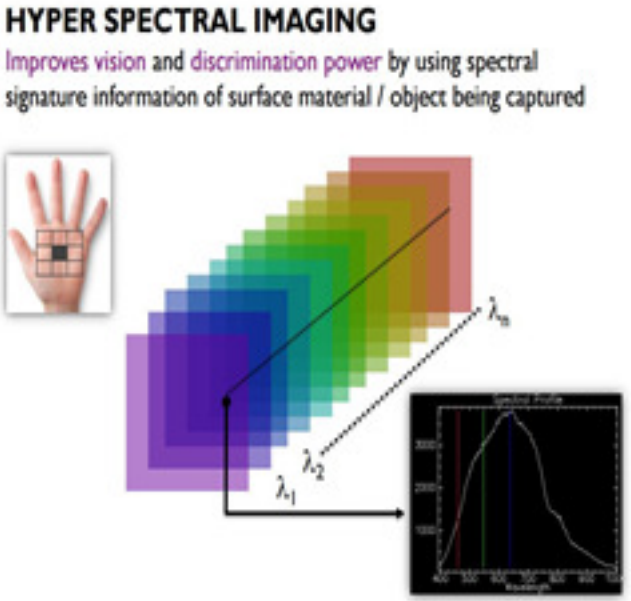
2

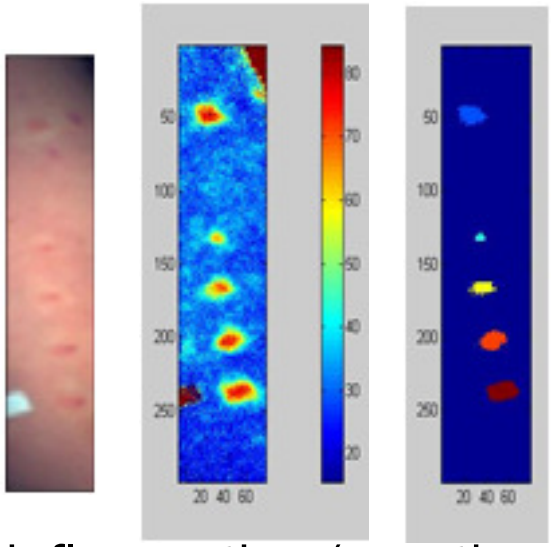
3

4

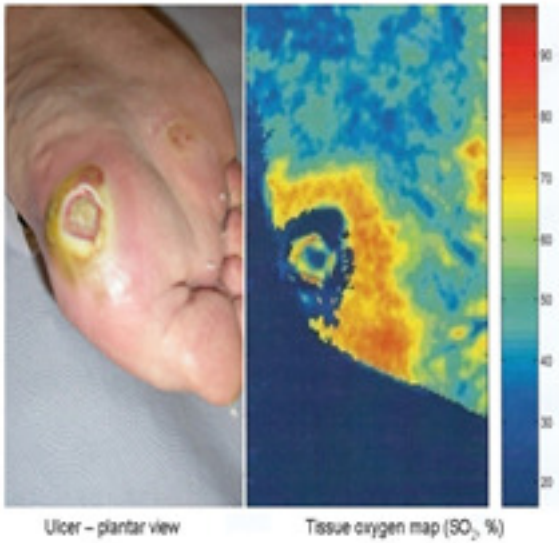
Hyperspectral Imaging for TOS mapping







Skin inflammation / reaction

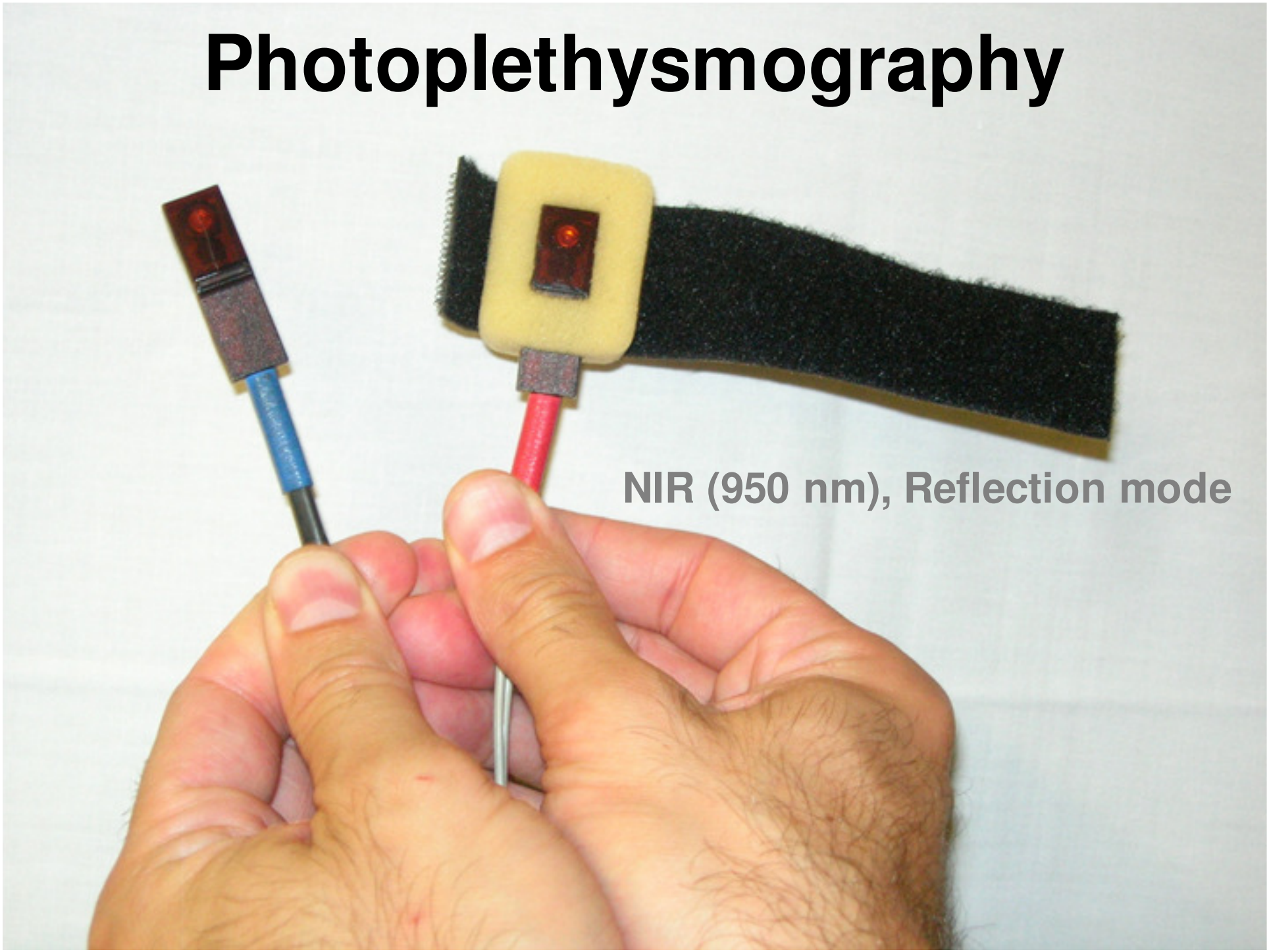


Diabetic foot ulcers

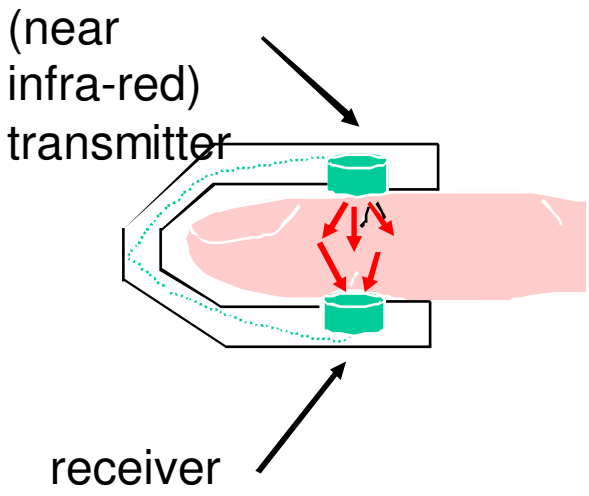
Photoplethysmography (PPG)

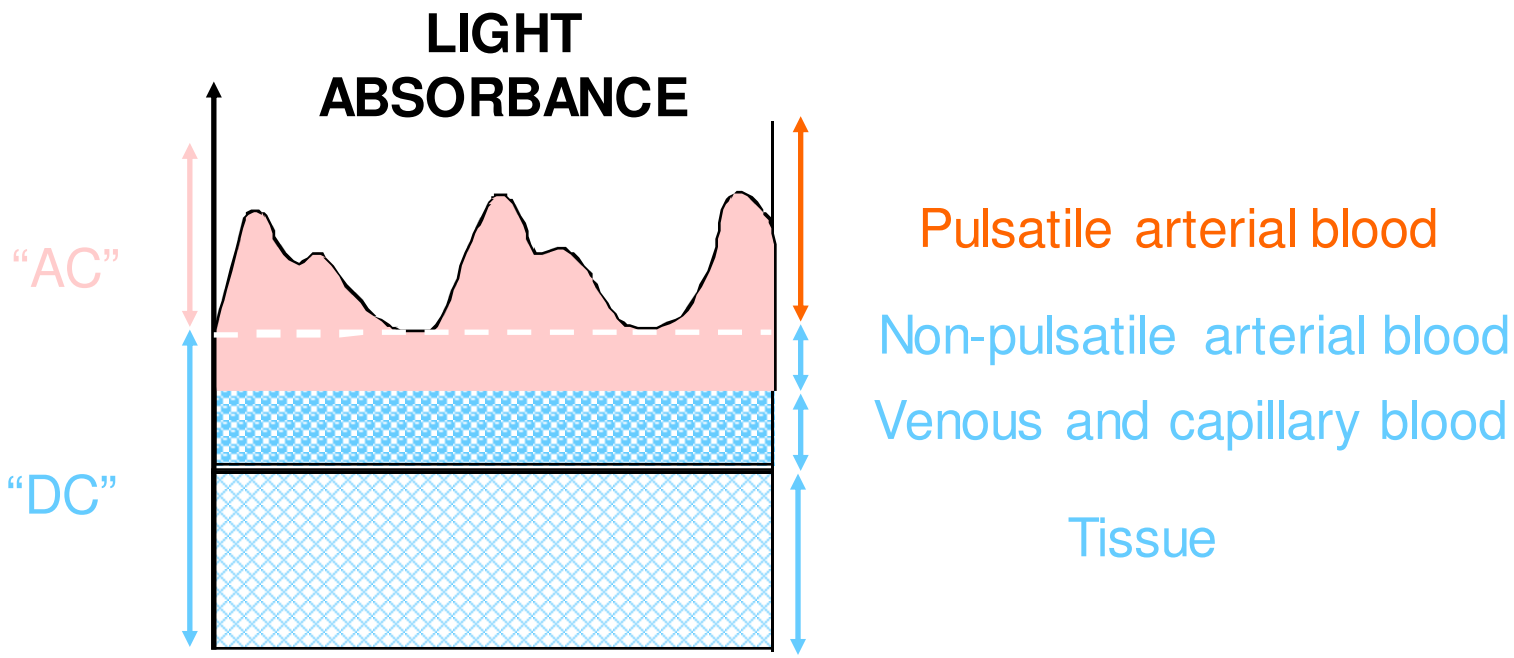
and
Imaging PPG (= iPPG)

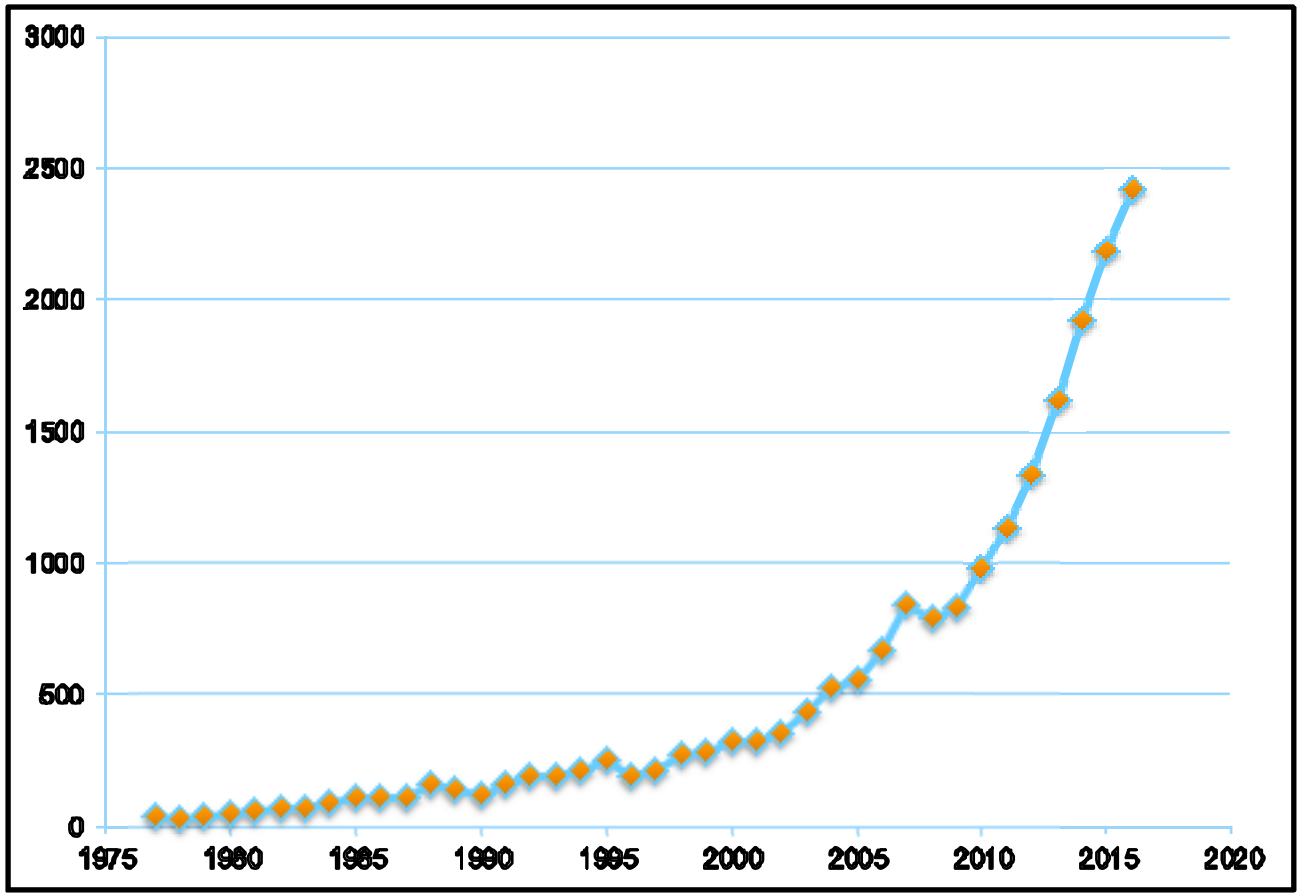
Photoplethysmography



PPG =


(near
infra-red)
transmitter
receiver


LIGHT
ABSORBANCE
"AC"
"DC"
Pulsatile arterial blood
Non-pulsatile arterial blood
Venous and capillary blood
Tissue

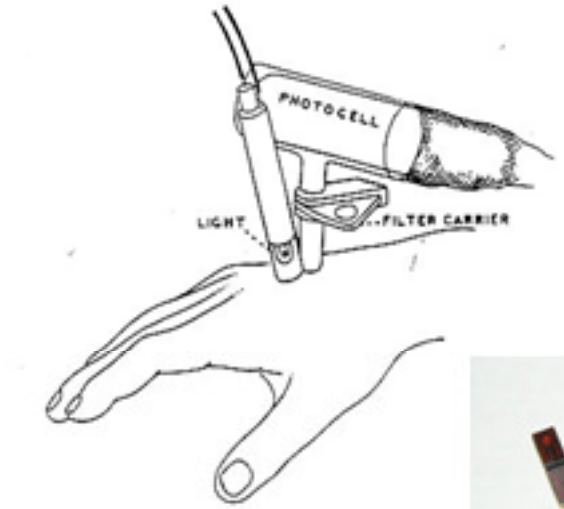


Photoplethysmography citations (Google Scholar)

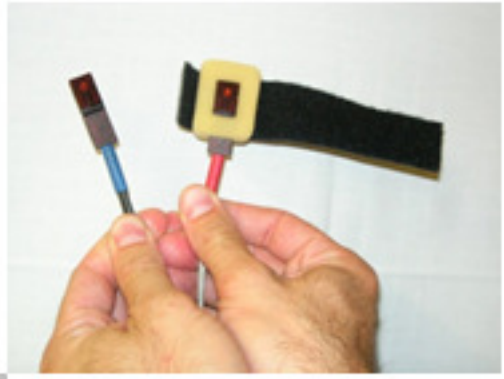
A. Clinical physiological monitoring
B. Autonomic function
C. Vascular assessment

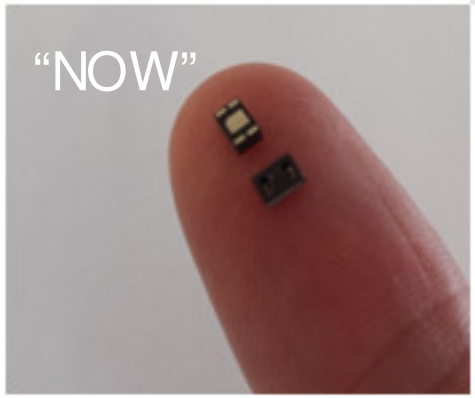
PPG: Smaller, faster, better, smart …

Sensors



- PPG = LED+PD, usually NIR.
- Modes? / Sites? / Attachment?
- Move to MINIATURE + DIGITAL

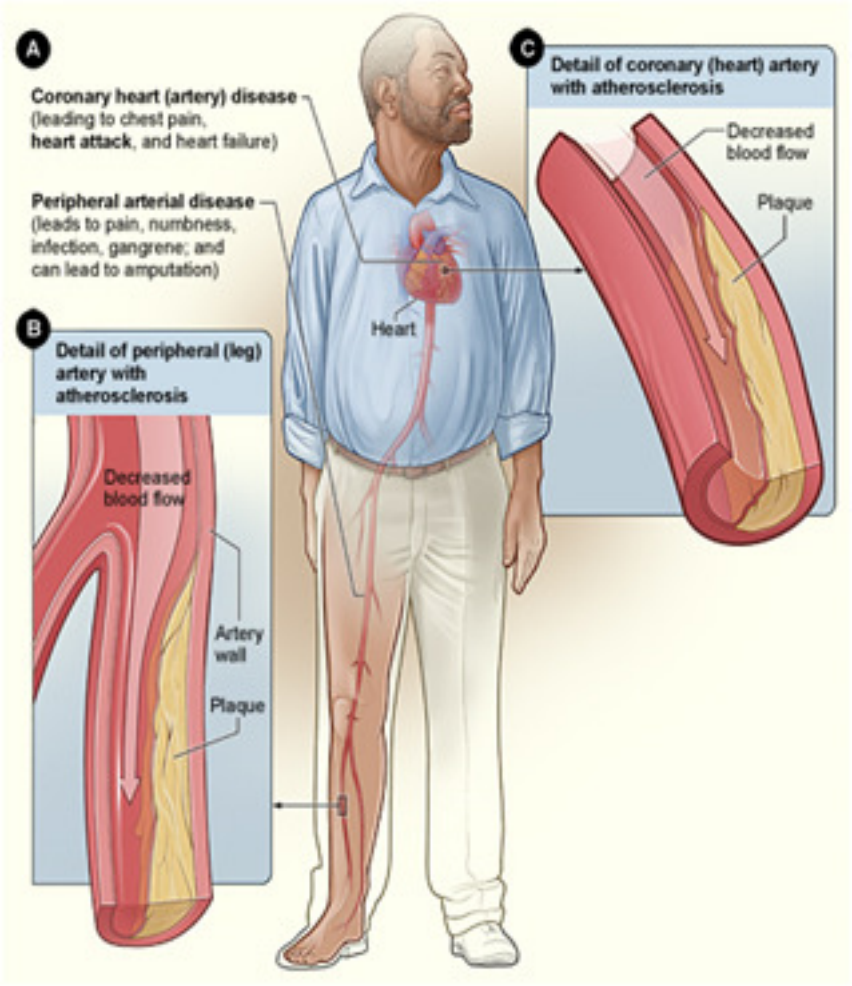


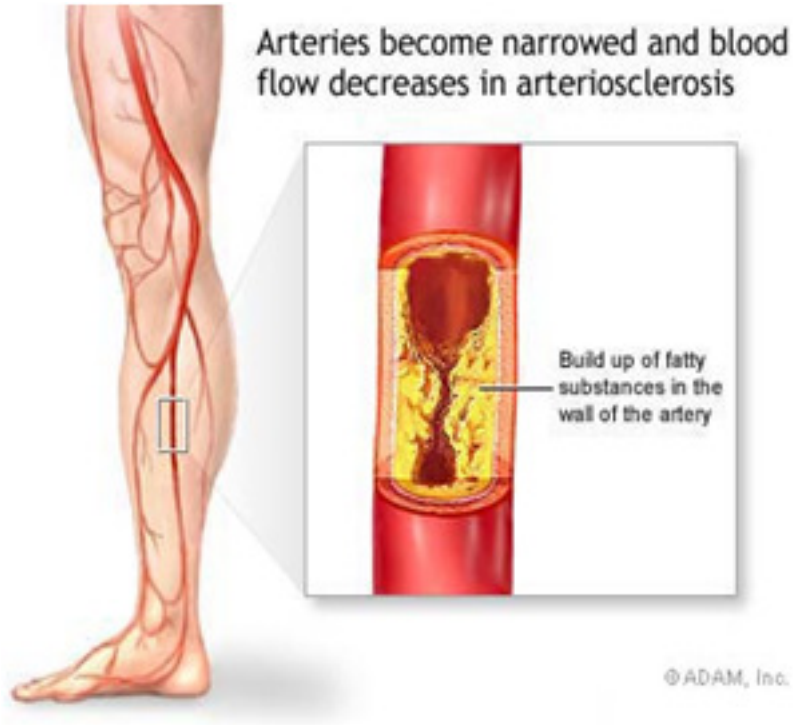


Processing / Output

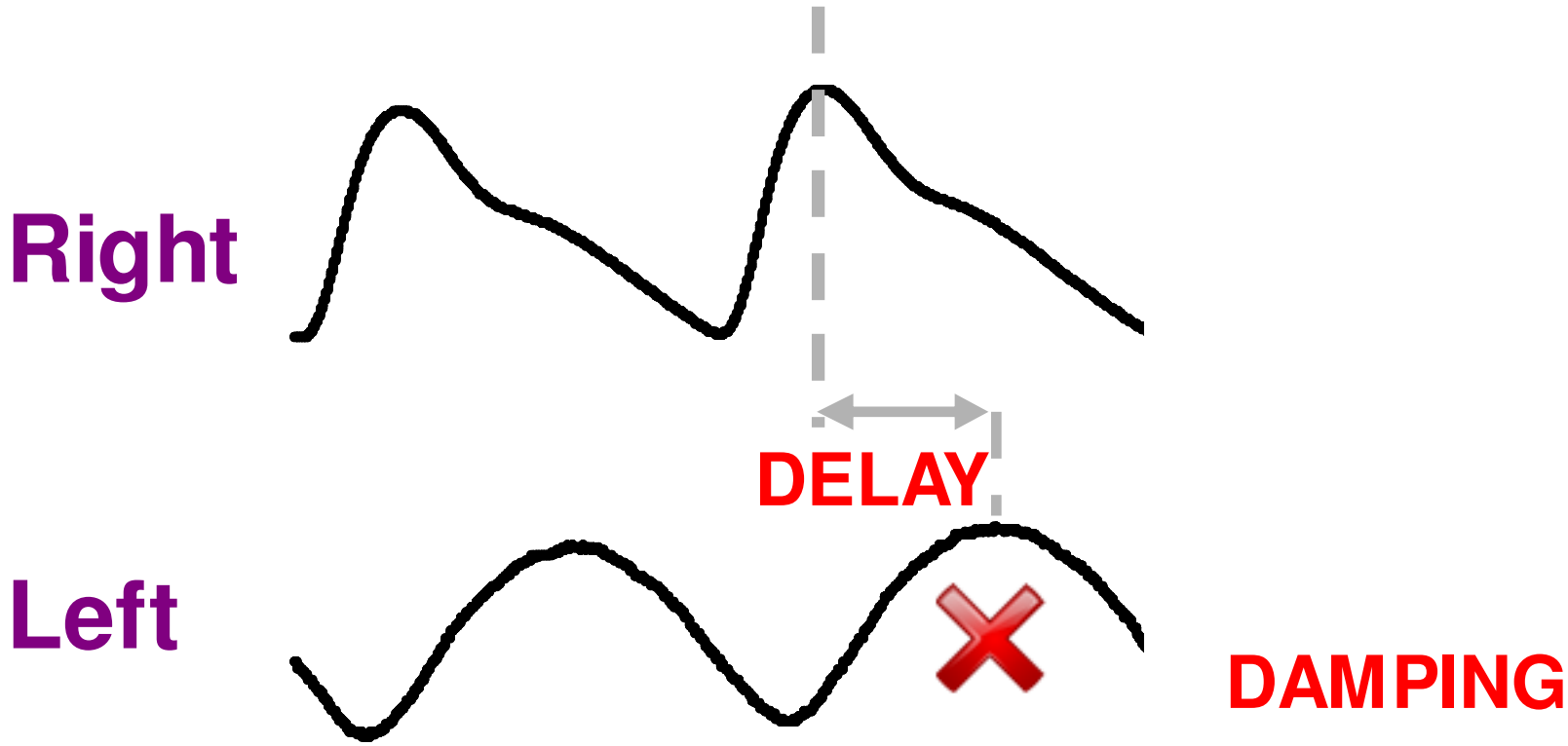
“ANALOGUE” early prototype

Peripheral Arterial Disease (PAD)





Pulse analysis: Unilateral PAD



The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Newcastle University

University of Sunderland

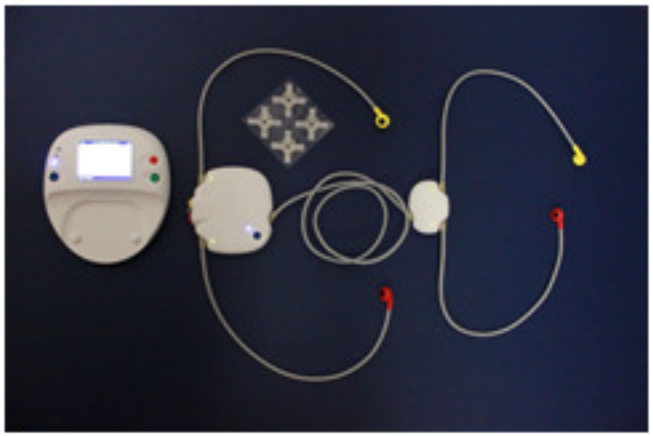
NHS
North of England Commissioning Support Unit

The *PulsePad* device for rapid assessment of peripheral arterial disease (PAD) in primary care

- **Problem:** PAD is a killer disease. Clinical need for patients to get accessible diagnostics in primary care.
- **Solution:** Develop *PulsePad* device + build case for adoption + commercialisation.
- **Design:** Automated, easy-to-use, quick, digital, informed ergonomics and aesthetics, production, scalability, IP.
- **Accuracy:** comparable with current PAD diagnostics i.e. the ABPI.
- NIHR i4i Cardiovascular Challenge funded ~£1.3M. Project 2014-17. NuTH / Medical Physics led by Dr John Allen and a multi-disciplinary team including Dr A. Sims and Professor G. Stansby. A journey to **"game changer"** impact.

Further information: john.allen@nuth.nhs.uk

PulsePad device with innovative pulse wave analysis to detect PAD



Bilateral PPG pulses:

Pulses damped & delayed in PAD

Uses our patented photoplethysmography (PPG) finger / toe pulse sensor design

Funded by NIHR

This slide is from independent research funded by the National Institute for Health Research Invention for Innovation (i4i) programme, "Innovative photoplethysmography technology for rapid non-invasive assessment of peripheral arterial disease in primary care", II-C1-0412-20003). The views expressed in this presentation are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

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15 November 2017

Nigel Fine
IET Chief Executive and Secretary

Nick Winser
IET President

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15 November 2017

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IET Chief Executive and Secretary

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IET President

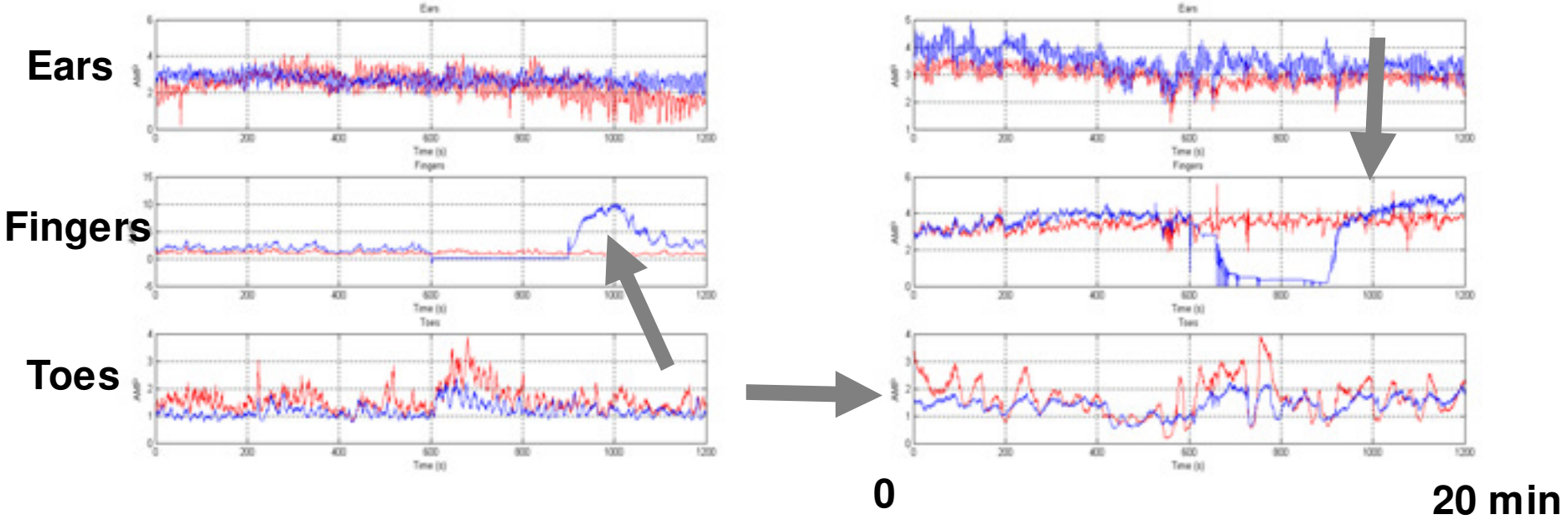
www.theiet.org/innovation

Recent IEEE EMBC visit ... ☺

- Hawaii – 3 posters presented.
- ~2700 delegates / 1000+ posters.

- 3 main themes: A) PPG, B) wearable sensors and C) deep learning …

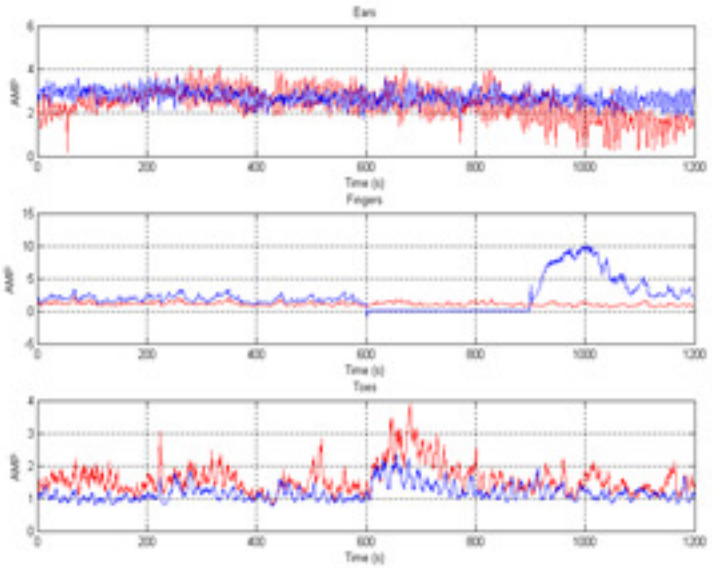
20 minute Cardiovascular study

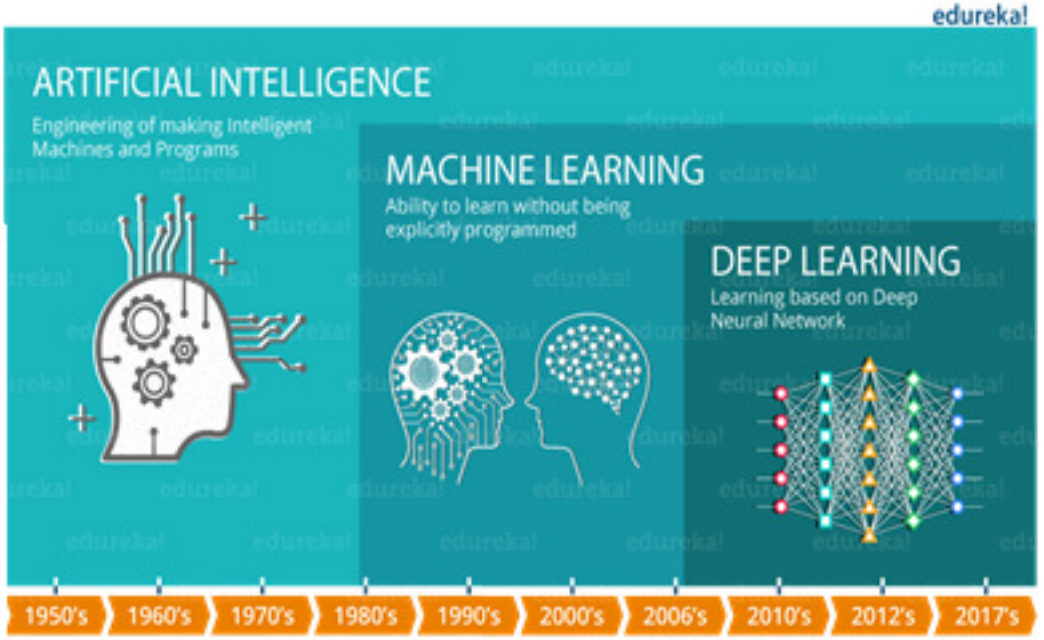


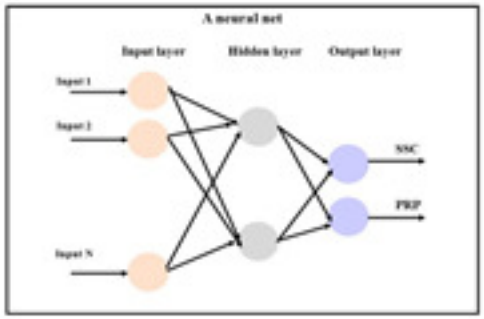
Normal **SSc**

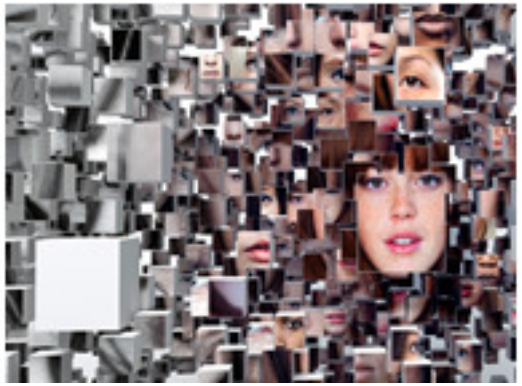
Assess: arterial stiffness, autonomic fn, PAD, and endothelial function

Deep Learning … in SSc for optical pulse

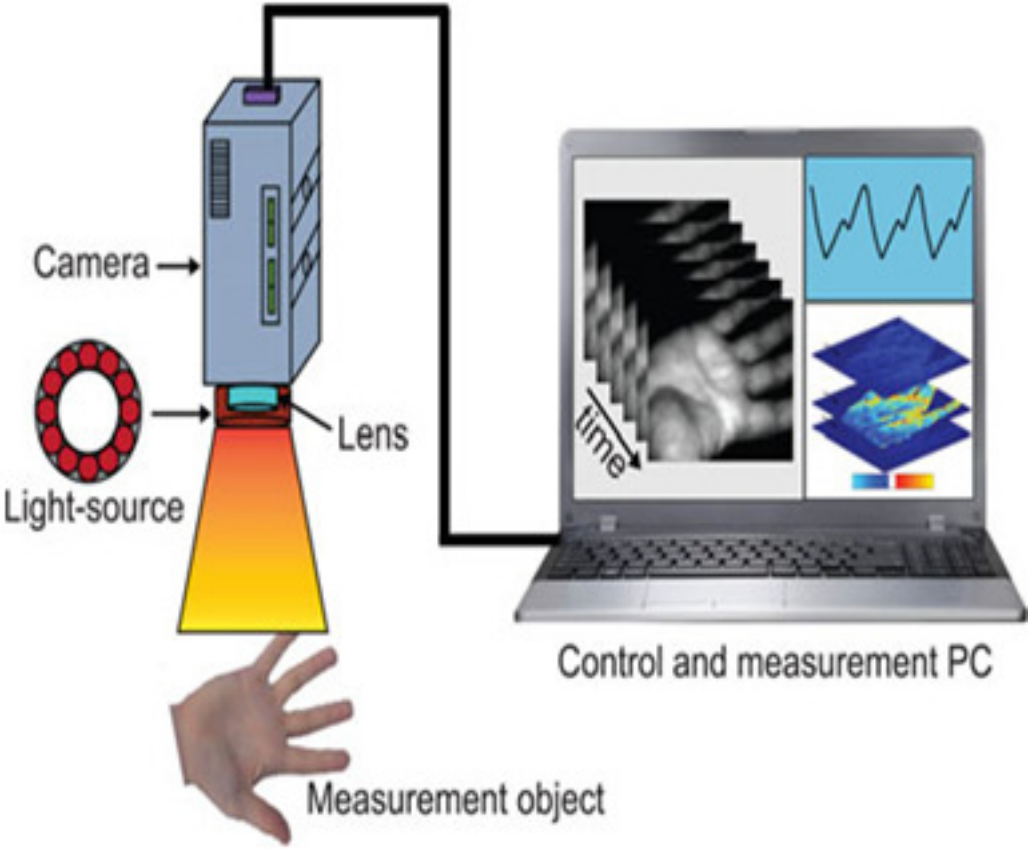




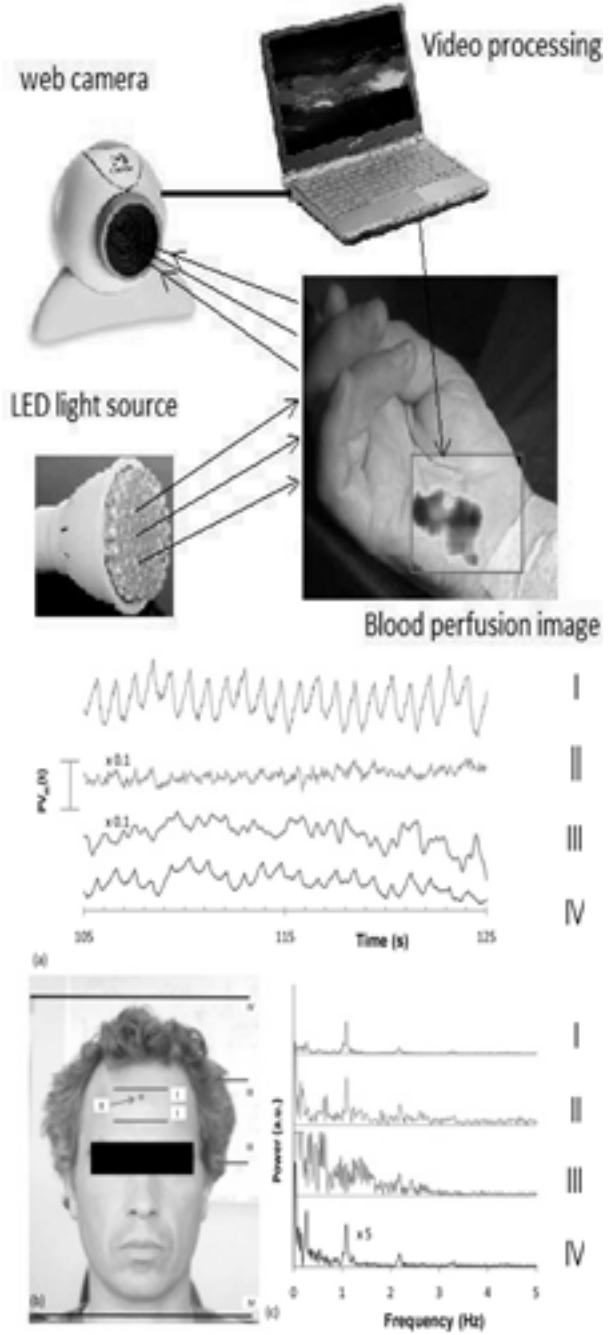




“iPPG”

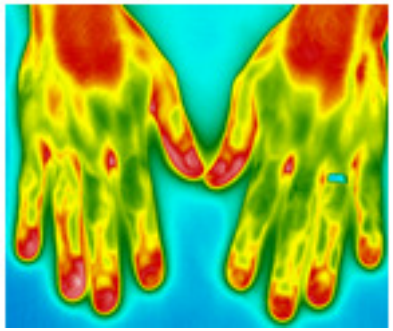


From Sun and Thakor 2015

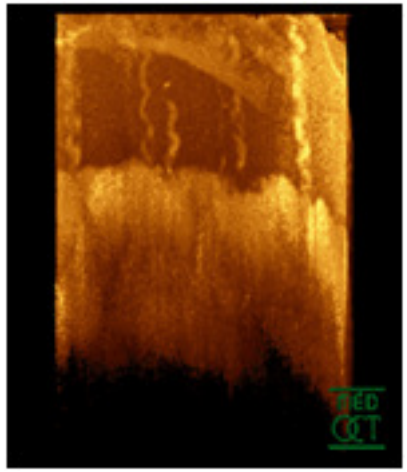


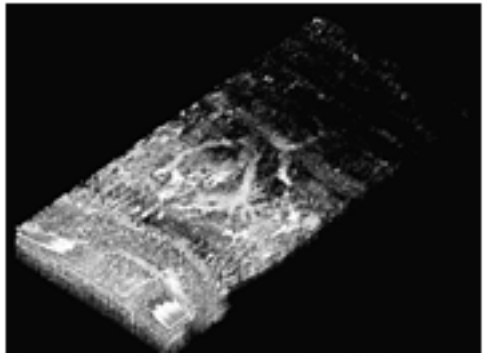
Summary

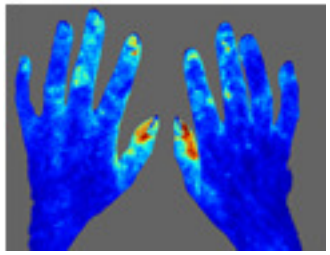
- Innovative measurement service and facilities overviewed.
- Currently, main imaging assessments: Thermal Imaging and Capillaroscopy.
- Overviewed also challenges, current linked R&D and many opportunities…

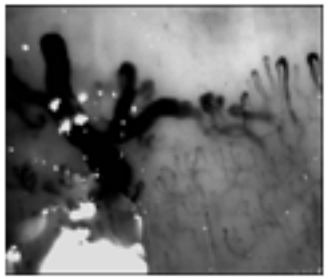


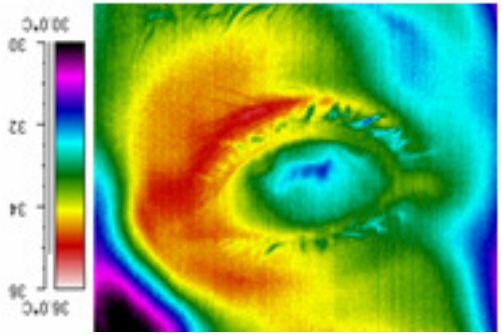
Thank you ...

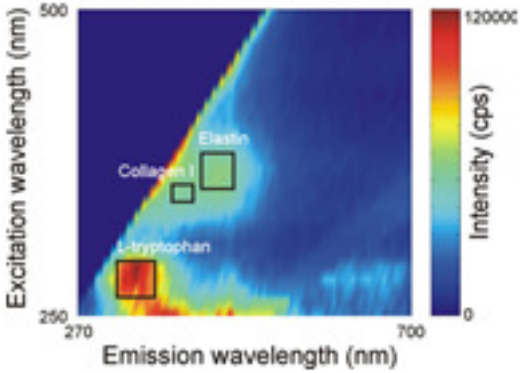


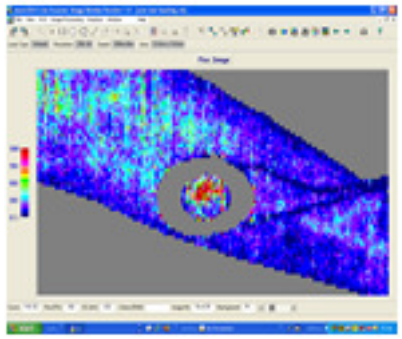


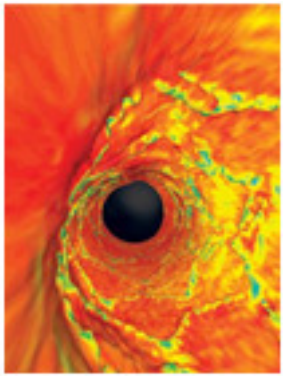


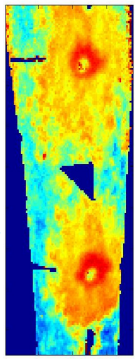


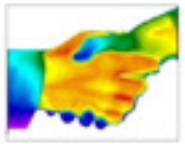


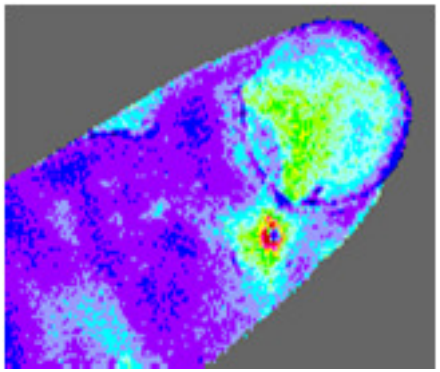

Skin fluorescence EEM
Excitation wavelength (nm)
500
250
270
700
Emission wavelength (nm)
Elastin
Collagen I
L-tryptophan
120000
0
Intensity (cps)

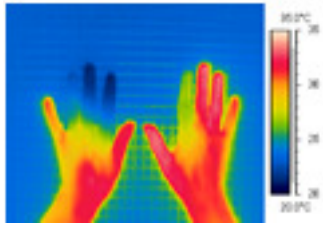


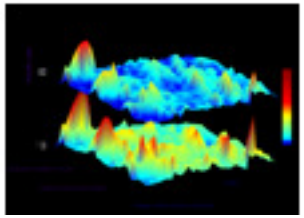


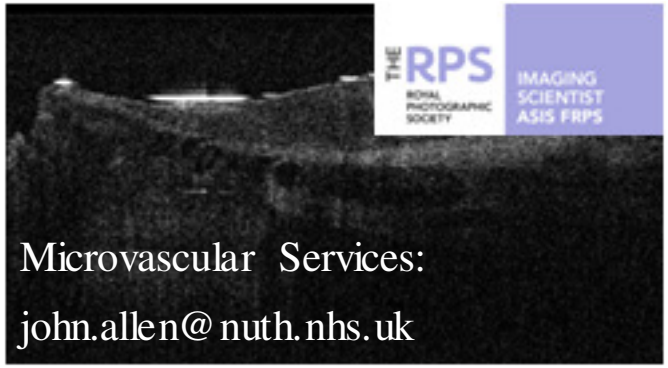








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