Age-related Increase in Videointensity of Normal Intima-Media Complex of the Common Carotid Artery in a Healthy Population

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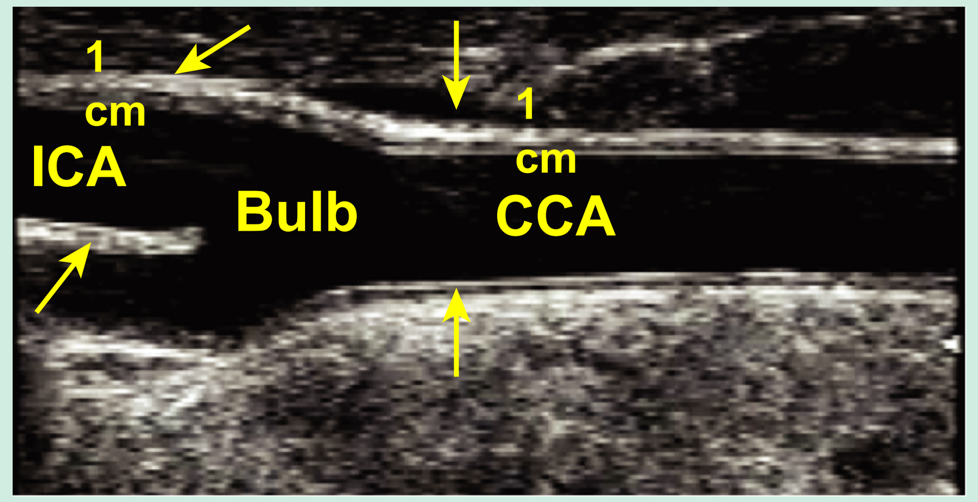
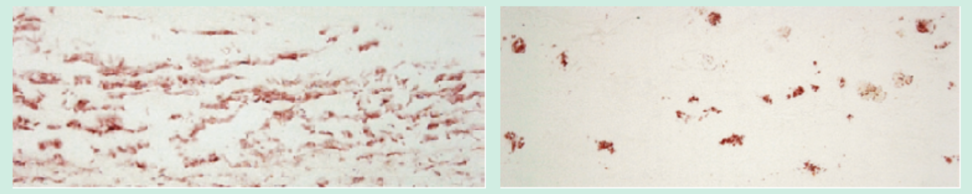
Background

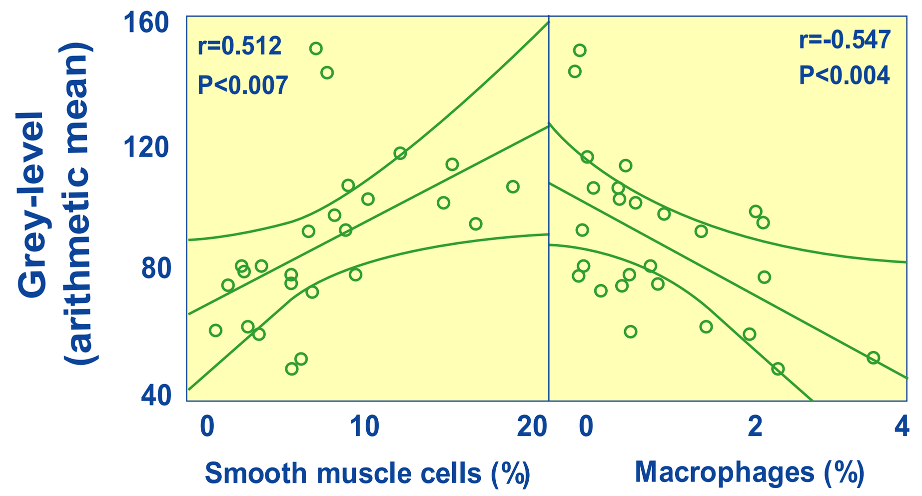
Aging…

- Is associated with intimal thickening of large arteries lacking the features of atherosclerosis[1]
- Exacerbates neointimal formation and increases proliferation of smooth muscle cells (SMCs), a normal component of the intima, in mice[2]
- Seems a major determinant of atherosclerotic progression[3]
- Is associated with a progressive increase in carotid intima-media thickness (IMT), in man[4]





Relationship Between Videointensity of Initial Atherosclerotic Changes and Its Cellular Composition



Puato M; J Vasc Sur 2003

Aim of Study

To explore relationships between videointensity of undiseased intima-media complex of the common carotid artery, and:

- IMT
- Age
- Risk factors for atherosclerosis

Study Population - RISC Population

Relationship Between **I**nsulin **S**ensitivity and **C**ardiovascular Disease Risk **(RISC)** Study

In the RISC study, 1,146 apparently healthy subjects were recruited in 19 centers in 14 European countries.

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RISC Study - Recruiting Centres

Pisa, London, Amsterdam, Newcastle, Lyon, Odense, Dublin, Perugia, Geneva, Frankfurt

Malmö, Rome, Glasgow, Wien, Madrid, Athens, Milan, Belgrade, Kuopio

Study Population

Age	≥30 and ≤60 years
Blood pressure	<140/<90 mmHg
Total cholesterol	<7.8 mmol/L
Triglycerides	<4.6 mmol/L
Fasting glucose	<7.0 mmol/L
2-hour glucose	<11.1 mmol/L

- Excluded: clinical cardiovascular disease, chronic diseases, carotid stenosis (>40%)

Study Protocol

- Lifestyle and medical history questionnaire
- Anthropometric measurements
- Biological samples including oral glucose tolerance test
- Ultrasound (US) examination of carotid arteries:
  1) Measurement of IMT of common carotid artery (CCA) far wall
  2) Videodensitometric analysis of intima-media complex (IMC) of CCA far wall

Methods

- Digitalisation of the CCA image in longitudinal projection with a resolution of 576 x 768 pixels and 256 grey level per pixel

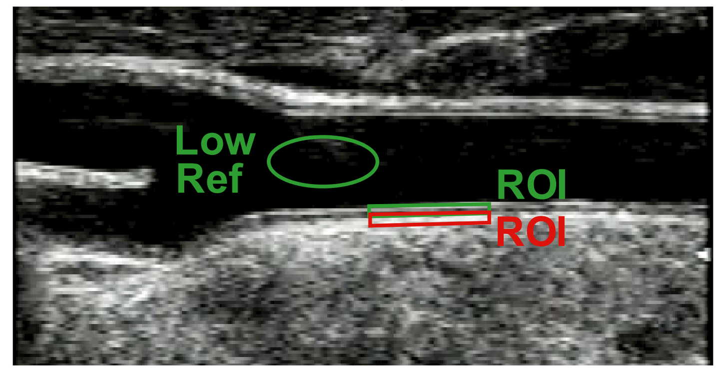
1) One region of interest (ROI, 0.4–1.0 x 2.0 mm) is placed at IMC, 1.5 cm before bifurcation

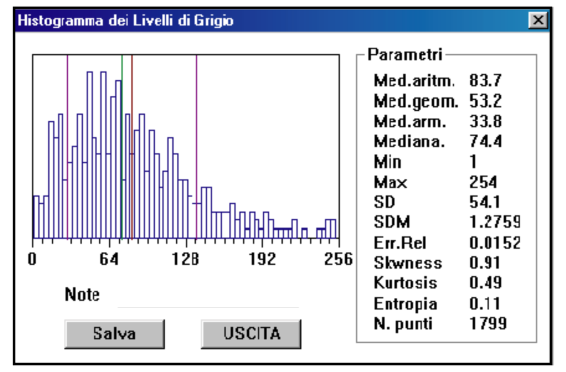
2) Second ROI is placed at adjacent adventitia

- A computer-driven image analysis system (Medical Image Processing [MIP], Institute of Clinical Physiology, CNR, Pisa, Italy) was used to analyse the ROIs by first-order (mean, standard deviation) statistical parameters
- **To adjust** for variable ultrasound **attenuation** and different **gain settings** in different subjects, **two calibration steps** were introduced:

1) The effect of the gain setting was restrained by calibrating the grey level amplitude of the ROI against the vessel lumen (blood) taken as the blank (mean grey value = 0)

2) The effects of imaging depth and attenuation were minimised by calibration against an internal reference represented by the adventitia





- Arithmetic mean grey level was computed in the IMC (GL-IMC) as well as in the adjacent adventitia (GL-Adv)
- The ratio of the mean grey level in the IMC and adventitia was calculated (GL- IMC/Adv) as an index of IMC video-intensity

Characteristics of Study Population

- In 874 of 1,146 subjects (76%) satisfying the inclusion criteria for the RISC Study it was possible to carry out video-densitometric analysis of undiseased CCA-IMC

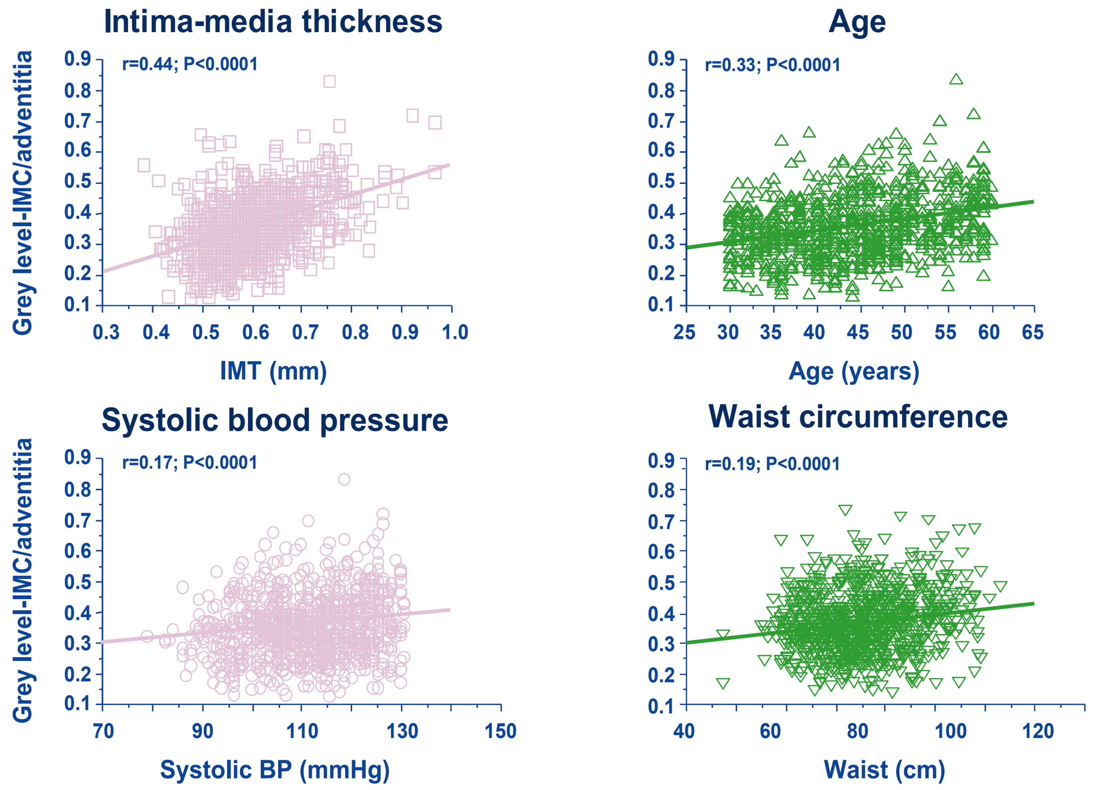
Male/female	378/496
Age (years)	44 ± 8
Smokers	450

	mean ± SD	range
Height	1.71 ± 0.1	(1.47–1.99)
Weight (kg)	73 ± 14	(44–127)
BMI (kg.m-2)	25 ± 4	(17–42)
Waist circ. (cm)	85 ± 12	(49–121)
Fat-free mass (kg)	53 ± 11	(36–92)
SBP (mmHg)	117 ± 12	(79–139)
DBP (mmHg)	74 ± 8	(50–89)
Total cholesterol (mmol/L)	4.8 ± 0.8	(2.8–7.2)
LDL-cholesterol (mmol/L)	2.9 ± 0.8	(0.8–5.4)
HDL-cholesterol (mmol/L)	1.5 ± 0.4	(0.6–2.7)
Triglycerides (mmol/L)	1.0 ± 0.5	(0.3–4.5)
Fasting glucose (mmol/L)	5.1 ± 0.6	(3.0–6.8)
Fasting insulin (pmol/L)	33 ± 19	(3–147)
CCA IMT (µm)	599 ± 88	(380–963)
Grey level-IMC/Adventitia	0.36 ± 0.10	(0.13–0.84)

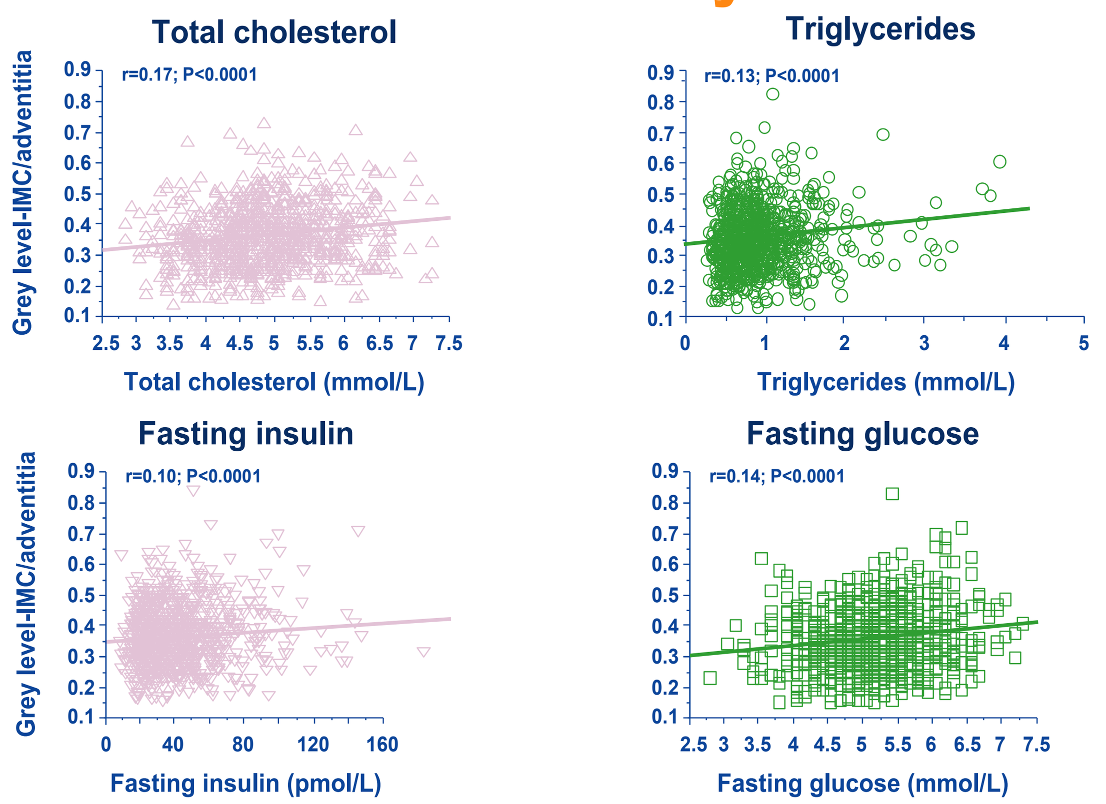
Main Determinants of CCA IMT

Age	+49 ± 3 µm per 10 years
Systolic BP	+22 ± 2 µm per 10 mmHg
LDL-cholesterol	+34 ± 4 µm per mmol/L
Sex	+36 ± 6 µm for male sex
Height	+14 ± 3 µm per 10 cm
Weight	+17 ± 2 µm per 10 kg
Waist	+22 ± 2 µm per 10 cm
Body mass index	+5.7 ± 0.8 µm per unit
Fasting glucose	+38 ± 5 µm per mmol/L
Fasting insulin	+0.7 ± 0.2 µm per pmol/L

Main Determinants of Intima-Media Videointensity



Main Determinants of Intima-Media Videointensity



Conclusions

In a healthy young to middle-aged European population, an **increased videointensity of the IMC parallels an age-related increase in IMT.**

This finding may indicate that, in the healthy IMC, **an increase in SMCs can contribute to an age-related increase in intima-media thickening** independent of risk factors for ATS, thus…

…confirming the hypothesis that **"subclinical disease of excessive IM thickening is not necessarily early atherosclerosis"[5]**

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EGIR-RISC Study Group

Project Management Board:
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Further information on the RISC project and participating centres can be found on www.egir.org.

References

[1]Stary HC et al "A Definition of the Intima of Human Arteries…". *Circulation* 1992;85:391–405;
[2]Vazquez-Padron RI, et al. *J Vasc Surg* 2004;40:1199–1207; [3]Stary HC, et al. *Circulation* 1995;92:1355–1374;
[4]Kiechl S, et al. *ATVB* 1999;19:1491–1498; Homma S, et al. *Stroke* 2001;32:830–835; [5]Lakatta EG, Levy D. *Circulation* 2003;107:139–146