

# Flow mediated vasodilatation A way to evaluate vascular healthiness with eTRACKING technology.



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## Introduction:

### From endothelium physiology to atherosclerosis...

Since the 80's, vascular endothelium emerged as a complex, local, regulating system of haemostasis, thrombosis and fibrinolysis, immunity, and vasomotricity. Most vessels (except capillaries) are under control of endothelium/smooth muscle complex (and probably adventitia) which allows local adjustment of calibre, as well as, resistance and distribution of the blood flow to the organs. This local control of the smooth vascular cells is mediated by the endothelium through the secretion of local vasorelaxing (e.g. nitric oxide or prostaglandin) or vasoconstrictor (e.g. endothelins,...) factors.

Atherosclerosis is a degenerative process of the vessel wall and function with aging. It is a primary cause of cardiovascular death in civilized countries. Currently, Most of our medical practices and diagnostics testing are aimed to detect and treat symptomatic vascular lesions, whereas, the need for an early detection of asymptomatic lesions and/or vascular dysfunction in primary care is emerging.

Thousands of papers have established that endothelial dysfunction seem to be the earliest detectable sign of atherosclerosis from youngsters to adults. This correlates with the classical risk factors (hypertension, tobacco, dyslipidemia, diabetes, etc).

Several methods have been proposed for the early detection of atherosclerosis, such as assessment of vessel stiffness (compliance), reactivity of the vascular endothelium to stimulating factors, remodeling of the vessels wall (e.g. intima-media thickness). Most are clinical research tools, although consensus appeals for use in clinical routine exams. To date, it is clinical challenge to evaluate endothelial function.

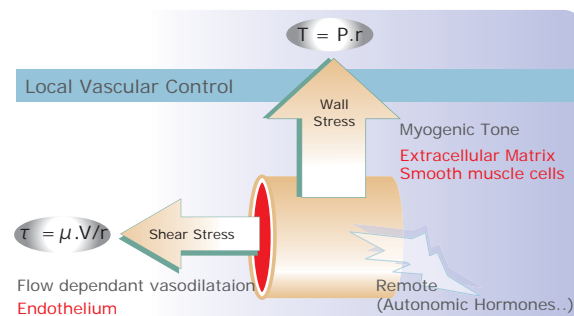


Fig1. vessel wall is subjected to parietal constraint (as expressed by tension = Pressure times radius). This is counteracted by myogenic tone and endothelial shear stress ( $\tau$ ), a function of the blood velocity (V), viscosity ( $\mu$ ) and radius (r). The local vascular regulation is under the hierarchical control of autonomic and hormonal regulation.

# Flow mediated vasodilatation

## A way to evaluate vascular healthiness with eTRACKING Technology

### Endothelial dysfunction: An early marker for atherosclerosis

First reports on vascular dysfunction were reported in the coronary vascular bed. Vasospasm could be paradoxically induced by local infusion of acetylcholine (an agonist for the endothelial mediated secretion of NO) in apparently healthy arteries (via angiogram). These findings were further demonstrated in peripheral arteries using venous occlusion plethysmographic techniques.

In 1992, Celermajer et al first reported a simple and non-invasive technique for the measurement of the endothelial dependent and independent vasodilatation (i.e. flow mediated dilation or FMD). The technique is based on the ultrasound measurements of the arterial diameter changes (generally brachial artery) resulting from an increase in blood flow velocity produced by a hand post ischemic hyperaemia. The increase in blood flow velocity is responsible for an increase in shear stress over the layer of endothelial cells. Experimental data suggest that this shear-stress induced-vasodilatation is mainly mediated by the production of endothelial derived relaxing factors (EDRFs), such as nitric oxide, by the endothelial cells. Since this pioneering study, a large number of publications revealed the pivotal role of endothelial dysfunction in a wide spectrum of vascular diseases in youngsters and adults long before a lesion develops.

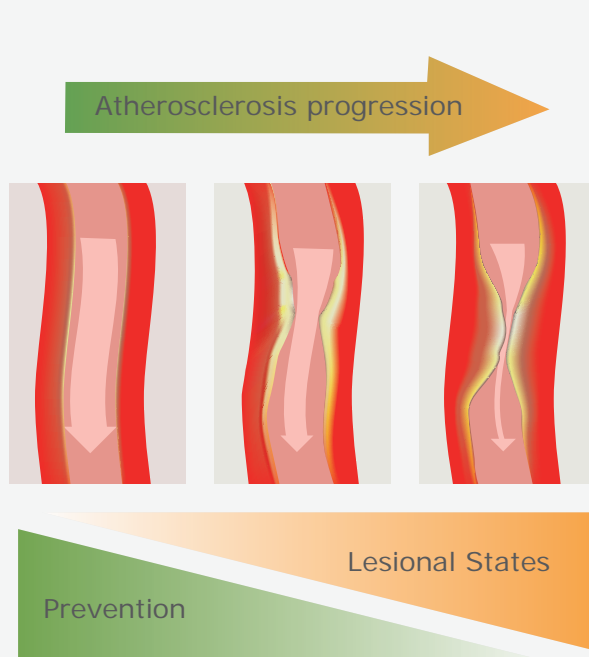


Fig2.

### How to assess the endothelial function with ultrasounds ?

The analysis of endothelial function is based on two basic principles:

- Induction of an endothelial-dependent response by a mechanical stimulus.

By means of an increase in shear-stress during a post-occlusive hyperemia.

- Induction of an endothelial-independent response by a direct stimulation of the smooth vascular muscle.

By means of a sublingual administration of nitroglycerine, a NO donor.

*i.e. Induction of an endothelial-dependent response by means of an agonist, requires an intra-arterial infusion of acetylcholine, which is an invasive method that cannot be proposed for routine investigations. Therefore, the mechanical stimulation of endothelium by the post-ischemic hand hyperaemia technique (cuff) has been acknowledged by the vascular community as the most relevant method to assess the endothelial dysfunction.*

### Endothelial function measurement with ultrasound technique require specific tools

- An ultrasound probe with a linear 7-10 MHz high spatial resolution allowing the detection of micrometric changes in diameter (radial artery diameter change measurement).
- A reliable RF signal tracking and a robust analysis software.

Although several studies have been performed using standard B-Mode imaging, M-Mode or echo-tracking (eTRACKING) are strongly recommended due to the significant higher spatial and temporal resolution of this mode (>0.001 mm).

- An immobilization of the arm/forearm with a probe holder is highly recommended to improve the measurement accuracy.

**Methods :**

1. The measures are performed on a resting subject/patients and should be done in a fasting state.
2. A flat, straight portion of the brachial artery is scanned (longitudinal view), with a clear delineation of both anterior and posterior intima-media interfaces. Side lobes and artefacts should be limited. It is optimal to maximally increase the distance between the probe and the artery by imaging the artery through the biceps muscle (see Fig 3).
3. A baseline diameter is recorded.
4. The wrist pneumatic cuff is then inflated 20 mmHg above systolic arterial pressure (not exceeding 200-210 mmHg) for 4 min.
5. The cuff is then deflated and the arterial diameter is recorded 1 min and 4 min after wrist cuff deflation.
6. Nitro-glycerine is administered (sublingual Natispray, 25  $\mu$  mg x 2).
7. The arterial diameter is recorded at 3 and 5 min while the arterial brachial pressure is measured (Fig 4).

With the software developed by ALOKA (ProSound  $\alpha$  10 /ProSound  $\alpha$  7) it is possible to select a discontinuous eTRACKING mode (e.g. separate sequences of 10-20s recording length\_Fig 5-1) or a continuous eTRACKING mode (up to 25 min of continuous data recording\_Fig 5-2). FMD (in % from baseline value) is expressed as the ratio of

post-ischemic maximal diastolic diameter change from baseline diastolic diameter to baseline diastolic diameter. It represents the endothelial independent vasodilatation.

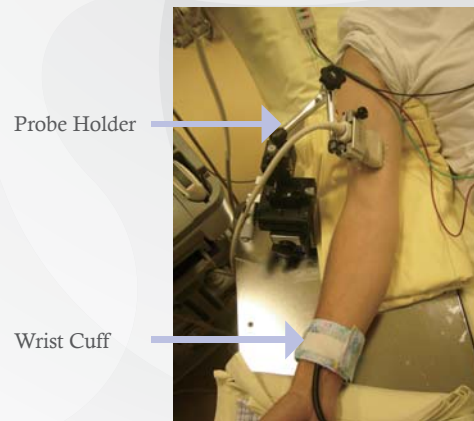


Fig3.

**Results & normal values :**

Data (see Fig 6) from our laboratory have been collected in 36 patients without cardiovascular risk factors (CVR=0: 16 males, mean age 47+/-2 yrs) and 44 patients with more than one cardiovascular risk factor (CVR>0: 35 males, mean age 60+/-2 yrs). Mean brachial diameter at rest was significantly larger in CVR>0 than in the CVR=0 group (4.4 +/-0.1mm versus 3.8 +/-0.1mm, P=0.001) with a reduced flow mediated dilatation (6.36+/-0.47% versus 9.26+/-0.96%, P=0.006).

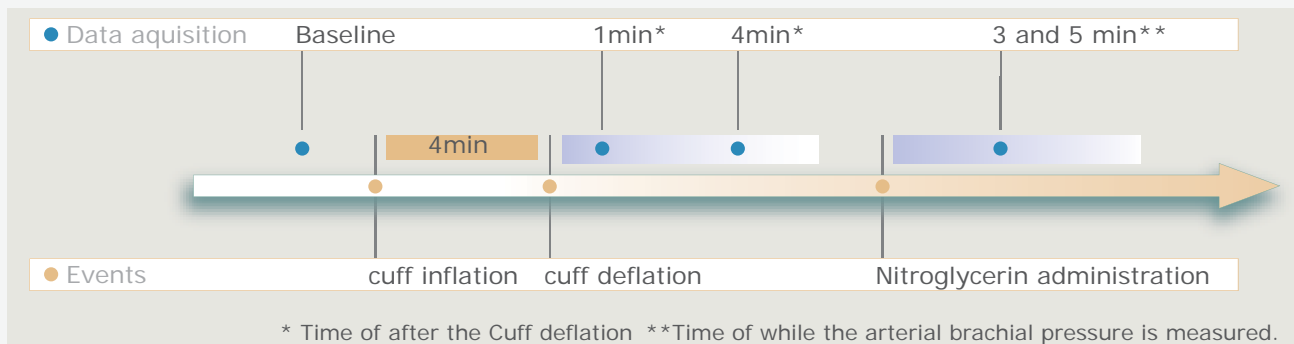


Fig4. Protocol of FMD



ProSound  $\alpha$  7



Fig5-1.



Fig5-2.

Inter-observer variability was 1.37 % and inter-sessions variability was 75%. Arterial diameter is systematically larger in patients due to arterial remodelling compared to controls. Brachial diameter changes from baseline show large variability in all groups. There was a significant increase from baseline diameter at 1min and 4 min post in both groups and a significant difference for each diameter between groups.

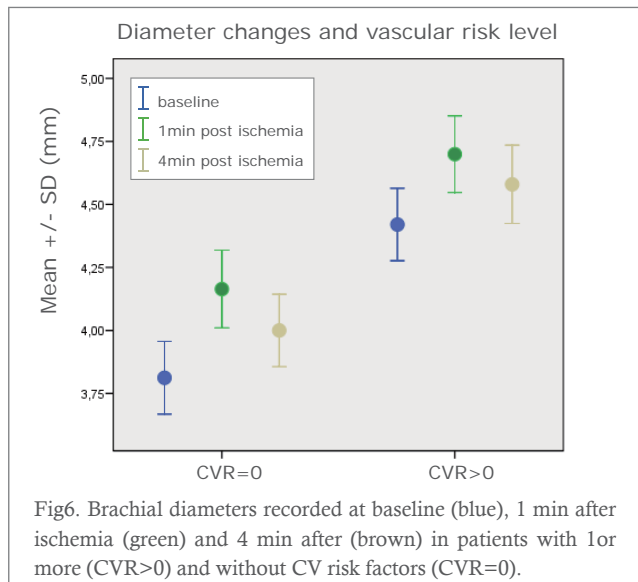


Fig6. Brachial diameters recorded at baseline (blue), 1 min after ischemia (green) and 4 min after (brown) in patients with 1 or more (CVR>0) and without CV risk factors (CVR=0).

There is abundant literature reporting normal values (i.e. control population of case-control studies). In healthy people, FMD ranges from 5% up to 15%. Subject standard deviations of 2.8% have been reported with coefficient of variation of 50% of the mean response. FMD is dependent of numerous factors such as nutritional states, exercise, genetics and circadian changes.

A non-negligible approximate results arise from the cumulative errors entailing the measurements are as follows:

**Small changes (almost undetectable) of the studied arterial segment.**

A 10% diameter change of a 4.5 mm diameter artery represents less than 0.5 mm of changes within-the image that can easily result from arm motion. The situation is sub optimal when the FMD changes reach 3-5%. To limit this bias, we suggest performing a late recording (e.g. at 4 min after cuff deflation). This late value can help check the diameter changes that are likely physiological rather than artefacts (i.e. should not be lower than baseline diameter).

**Variable endothelial stimulus.**

Shear stress is quickly changing during the post ischemic period. Therefore, the "input" (controlled by the regional autonomic and hormonal regulation to the endothelium) is also changing. Purposely, normalization with the changes in velocity (from pre-ischemic baseline values) is suggested and recommended. However, it should be remembered the true stimulus is shear stress (a function of velocity and diameter).

**It is not possible to determine the "resting diameter" of an artery.**

This point is important, and unfortunately, sometime neglected as it will affect the range of changes in arterial diameter. Determination of the maximal vasodilatation by the use of direct vasodilator (such as NTG) could help to determine the range capabilities of the diameter changes of the studied artery.

**Almost 62 subjects per groups of studied subjects are required to detect a FMD difference of 2% (De Roos et al).**

**Conclusions:**

Determination of the endothelial function provide indisputable information in the individual staging of the "vascular patient's age".

Ultrasound methods based on echo-tracking technology, such as Aloka's eTRACKING technology, provide a unique, precise and reliable tool. Great caution should be accorded to the measured data. Hence, the potential interest of this investigation method remains to be determined in the individual staging of the vascular arteriosclerosis.

**References:**

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